A CLINICO-EPIDEMIOLOGICAL STUDY OF ORAL LESIONS IN ACQUIRED BULLOUS DERMATOSES

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CERTIFICATE

This is to certify that the dissertation entitled **"A CLINICO-EPIDEMIOLOGICAL STUDY OF ACQUIRED BULLOUS DERMATOSES''** is a bonafide work done by **Dr. J. Jayasri**, at Madras Medical College, Chennai in partial fulfilment of the university rules and regulations for award of M.D., Degree in Dermatology, Venereology and Leprology (Branch-XX) under my guidance and supervision during the academic year 2009 -2012.

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DECLARATION

I, **DR. J. JAYASRI,** solemnly declare that dissertation titled, "**A CLINICO-EPIDEMIOLOGICAL STUDY OF ORAL LESIONS IN ACQUIRED BULLOUS DERMATOSES"** is a bonafide work done by me at Department of Dermatology and Leprosy, Madras Medical College, Chennai-3 during the period of October 2009 to September 2011 under the supervision of **Prof. DR.S.JAYAKUMAR, M.D, D.D,** Professor and HOD, The Department of Dermatology and Leprosy, Madras Medical College, Chennai. The dissertation is submitted to Tamilnadu Dr. M.G.R. Medical University, towards partial fulfilment of requirement for the award of **M.D. Degree (Branch-XX) in DERMATOLOGY, VENEREOLOGY AND LEPROLOGY**.

(Signature of the candidate)

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Introduction

INTRODUCTION

Oral cavity occupies a unique position in the human body. As it is situated anatomically between the skin externally and the intestinal mucosa internally, it shows some properties of each in various aspects. Hence it can act as a marker of both cutaneous as well as internal diseases. A number of diseases affect both skin and the oral mucosa and in some, the oral involvement precedes the skin disease and can well help the disease to be identified earlier thereby making the management feasible at an earlier course of the disease, thus reducing the morbidity of the disease considerably.

The oral mucosa differs from the skin anatomically in several aspects. With the exception of the dorsum of the tongue and the hard palate, stratum corneum and stratum granulosum are not present in the mucous membrane of the mouth. Where these layers are absent, the epithelial cells appear vacuolated as a result of their glycogen content. The epithelial cells of the oral mucosa show only few well-developed desmosomes and instead, they show numerous microvilli at their borders.[1]

A careful scrutiny of the oral mucosa becomes an essential and integral part of dermatological examination, especially when it comes to

vesiculobullous dermatoses. Autoimmune vesiculobullous disorders, in particular, more frequently affect the oral cavity in a severe manner affecting the oral intake and general nourishment of the body which in turn increases the morbidity.

The interpretation of signs and symptoms in oral cavity poses difficulty due to its anatomical and functional properties. The vesicular lesions easily rupture leaving erosions. Painful nature of most of the vesiculobullous lesions leads to difficulty in maintaining proper oral hygiene. The ulcers get easily infected and consequently become foul smelling.

Thus it is important to know the various oral manifestations of vesiculobullous disorders in order to facilitate an early diagnosis and treatment which will pave way for significant reduction in the morbidity.

Review of Literature

REVIEW OF LITERATURE

Blistering conditions of the oral mucosa can be due to trauma, infection or immune-related diseases. The various vesiculo bullous dermatoses involving both skin and oral cavity are classified as follows.[2,3]

1. Viral infections:
   - A. Herpes simplex virus
     - i) Primary gingivostomatitis
     - ii) Recurrent herpes stomatitis
     - iii) Recurrent herpes labialis
   - B. Varicella zoster virus
     - i) Primary varicella
     - ii) Herpes zoster
   - C. Cox Sackie virus
     - i) Hand foot and mouth disease
     - ii) Herpangina
2. Autoimmune blistering disorders:
   - A. Intra epidermal blisters:
     - i) Pemphigus vulgaris
     - ii) Pemphigus vegetans
     - iii) Paraneopalstic pemphigus

iv) Pemphigus foliaceous

v) Pemphigus erythematosus

vi) IgA pemphigus

B. Subepidermal blisters:

i) Bullous pemphigoid

ii) Epidermolysis bullosa acquisita

iii) Mucous membrane pemphigoid

iv) Dermatitis herpetiformis

v) Linear IgA disease

vi) Bullous lupus erythematosus

vii) Bullous lichen planus

3. Drug eruptions:

i) Erythema multiforme (can be drug & virus induced)

ii) Stevens Johnson syndrome

iii) Toxic epidermal necrolysis

iv) Bullous fixed drug eruption.

VIRAL INFECTIONS

Herpes simplex:

A variety of infections of the oral cavity are caused by herpes simplex viruses, commonly type I and rarely type II.[4,5] These infections

may be primary or inoculation infections or secondary or recurrent infections. Chronic infection of oral and perioral tissues can occur in immunocompromised individuals.[6]

Clinical features: Herpes simplex labialis, also known as cold sores or fever blisters, is the most common presentation characterised by recurrent episodic lesions that arise at the muco-cutaneous junction as grouped papules on an erythematous base which progress to vesicles, pustules, erosions and scab. The lesions heal over 7-10 days without scarring.[7]

Primary herpetic gingivostomatitis is a self limited acute infection, occurring most frequently in the first two years of life but can occur at any age in those with no prior exposure to the virus.[7,8] Patients are ill with fever, malaise, pain & excessive salivation. The oral lesions characteristically affect the interdental papillae first, causing erythema, edema and hemorrhage. Lesions rapidly progress to involve the other areas in the mouth and lips causing a diffuse painful stomatitis. The regional lymph glands are enlarged and tender. The fever subsides after 3-5 days and recovery is complete in 2 weeks.[9]

Recurrent intraoral herpes simplex virus infections are rare. In this, the lesions are grouped and affect the well keratinised mucosa overlying

the hard palate or alveolar ridges & areas of trauma. They occur in an episodic fashion similar to recurrent herpes simplex labialis.[10]

Chronic indolent lesions, usually ulcerative or nodular, may be seen in neutropenic, immunosuppressed and chronic leukemia patients.[11]

Histopathology: Earliest specific finding is the nuclear changes in the epidermal cells, including peripheral clumping of chromatin, homogenous 'ground glass' appearance and ballooning of nuclei. Combined mononuclear and polymorphonuclear infiltrate is seen. Vacuolization is the earliest cytoplasmic alteration. Late lesions show the eosinophilic intranuclear inclusion bodies and a dermal infiltrate of numerous neutrophils. Vesicles appear secondary to cell degeneration (secondary acantholysis).[1,2]

Chicken pox:

Primary varicella or chickenpox, caused by Varicella zoster virus, usually occurs in children aged 3-6 years, who are not immunized at the time of their first exposure to the virus. Prodromal symptoms like fever and myalgia occur. Itchy papules appear in crops over the trunk and then spread to the head and extremities. They transform into stages of vesicle, pustule, erosion and scab. This is followed by antibody production and convalescence. The virus usually becomes latent in the dorsal root

ganglia. In the oral cavity, it may present with a few vesiculopustules on the oral mucosa, particularly on the soft palate, uvula or the anterior tonsillar pillar but without gingival involvement.[12]

Herpes zoster:

Herpes zoster affecting the maxillary or mandibular divisions of the trigeminal nerve, glossopharyngeal nerve or the geniculate ganglion may cause oral lesions. Oral ulcers appear in the distribution of the involved branch of the nerve.[13]

When the mandibular branch is involved, lesions are seen over ipsilateral half of the tongue, floor of the mouth, lower labial and buccal mucosa whereas palate, upper gingivae and the buccal sulcus are involved in maxillary branch zoster.[14]

Ramsay-Hunt Syndrome, characterised by unilateral facial palsy with vesicles and ulcers in the ipsilateral ear, soft palate and anterior 2/3rd of the tongue results due to involvement of the geniculate ganglion of facial nerve.[14]

Glossopharyngeal zoster produces pain in the ear and pharynx, with vesicles and ulcers on the soft palate and the ear.[12]

Microscopy: Histopathological features are similar to herpes simplex except for the more pronounced vascular changes.[1,2]

Hand, foot and mouth disease:

Hand, foot and mouth disease is a relatively rare, benign self limiting, highly contagious viral infection, mainly affecting infants and children. No racial or gender predilection has been recognised. The first Indian epidemic was recorded in Kerala in 2003.[15]

Aetiopathogenesis: Coxsackie viruses, enteroviruses and the echoviruses are the causative agents of which Coxsackie A16 and Enterovirus 71 are the most commonly implicated agents. Transmission occurs by aerosolised droplets, fecal, feco-oral and oral-oral routes.[16]

Clinical features: One or two days after the onset of prodromal symptoms, painful sores or papulovesicules with perilesional erythema, develop in the oral cavity usually on the tongue, palate, gums and buccal mucosa. Skin rash develops over 1-2 days[15] consisting of flat or raised red spots, sometimes with blisters surrounded by erythematous halo on the palms, soles, buttocks and rarely over knees and genitals. Lesions in the palms and soles are elliptical with their long axis parallel to the skin lines.[15] By the 7^{th} day, the titre of neutralising antibodies increase and the virus is eliminated.[16]

Herpangina:

Herpangina is an acute febrile illness caused by Coxsackie virus. Coxsackie virus A16, Coxsackie virus B and Enterovirus 71 have been implicated most often. Less common causes include echovirus, parechovirus 1, adenovirus, and Herpes simplex virus (HSV).[17,18]

Clinical features: Herpangina typically occurs during the summer and usually develops in children aged 3-10 years, occasionally occurring in newborns, adolescents and young adults without any sexual predilection. It is characterised by malaise, anorexia, irritability, low grade fever, slightly enlarged & tender anterior cervical lymphadenopathy and papulovesicular grouped eruptions or ulcerative lesions in the oropharyngeal mucosa, especially on the soft palate and uvula (enanthem). Occasionally lesions may occur on the tongue and posterior buccal mucosa. The ulcers may persist for up to one week, even after the fever has subsided. [19]

It can occur in association with enteroviral exanthem, aseptic meningitis, encephalitis, acute flaccid paralysis and other clinical syndromes. Diagnosis is clinical. Laboratory studies are generally not indicated as it is a mild and self-limiting illness. No histopathologic

findings are specific to herpangina. Isolation of the virus by culture can confirm the diagnosis.[20]

Differential diagnoses include aphthous stomatitis, acute retroviral syndrome, Hand-Foot and Mouth Disease, Herpes Simplex, Infectious Mononucleosis, bacterial and viral pharyngitis. [20]

AUTOIMMUNE BLISTERING DISORDERS:

Pemphigus is a group of potentially life threatening autoimmune diseases characterized by cutaneous and/or mucosal blistering.[21] Pemphigus can be classified into six types: pemphigus vulgaris, pemphigus vegetans, pemphigus erythematosus, pemphigus foliaceus, paraneoplastic pemphigus and IgA pemphigus.[22]

Pemphigus vulgaris:

It is the most common variant that presents with oral lesions as an initial manifestation in 50% of cases.[23] It affects only 1-5 patients per million population per year.[24] The peak incidence of pemphigus vulgaris occurs between the fourth and sixth decades of life with a male to female ratio of 1:2.[25]

Pathogenesis: The precise pathogenesis of pemphigus vulgaris is not clear. Autoantibodies directed against desmoglein 1 & 3 are the main

underlying factors in the pathogenesis which interfere with the cell-cell adhesion function of the desmosomes leading to loss of cell-cell cohesion (acantholysis) either directly by steric hindrance or it may be mediated by signal transduction. Proteinases, likely induced by pemphigus antigen-antibody complex, are thought to play an important role in acantholysis.[1] Recent studies have shown that acantholysis can occur in the presence of auto antibodies against 9 alpha nicotinic acetylcholine receptor.[26]

Clinical features: Flaccid blisters filled with clear fluid arise either on normal skin or an erythematous base over the scalp, face, axillae, groins and pressure points. These rupture and produce painful erosions that extend at the edges in an irregular manner. Gentle lateral pressure on unaffected skin or margin of the lesion causes the epithelium to disintegrate and form a bulla or an erosion (Nikolsky's sign). Nearly all patients have mucosal lesions, and at the time of presentation oral lesions are seen in 50 to 70% of patients. These may precede cutaneous lesions by months or be the only manifestation of the disease.[27-29]

The oral lesions are characterized by blisters that rapidly rupture, resulting in painful erosions.[30] While any area in the oral cavity can be involved, the soft palate, buccal mucosa and lips are predominantly affected.[30] The buccal mucosa is the most common site, followed by

palate, lips, tongue and gingiva.[23,30] Nikolsky's sign is useful in demonstrating the reduced epithelial adhesion when no lesions are present on examination and to differentiate from other erosive lesions.[2]

Other mucosal surfaces may be involved, including the conjunctiva, nasal, pharynx, larynx, oesophagus, urethra, vulva and cervix.[27]

A Tzanck smear taken from the floor of a fresh bulla or an early erosion shows acantholytic keratinocytes, arranged singularly or in clusters, with rounded, condensed cytoplasm and an enlarged nucleus with peripherally palisaded chromatin and enlarged nucleoli.[31]

Histopathology: Suprabasal bulla with acantholytic cells in the bulla cavity is the typical picture. The basal keratinocytes are separated from one another due to the loss of attachment, but remain firmly attached to the basement membrane like a row of tombstone.[1] Eosinophilic spongiosis may be seen in early cases. Older lesions will show intraepidermal bulla due to epithelial regeneration.[32]

Direct immunofluorescence study: Immunoglobulins especially IgG and complement are deposited in the intercellular space giving the characteristic “fish net” appearance.[5,27] It is usually positive in 100% of cases when the disease is active.[33,34] Spongiotic dermatitis, psoriasis,

bullous impetigo, and epidermis adjacent to ulcers secondary to a number of disorders may have squamous intercellular substance IgG due to insulation of serum into the intercellular substance.[1]

Other investigations: Indirect immunofluorescence studies enable a search for circulating auto antibodies in the patient's serum and are usually performed after direct immunofluorescence studies reveal the presence of antibody deposits in the mucosa. Specific enzyme linked immunosorbent assays (ELISA) and immunoblotting are also available for detecting desmoglein 3 and desmoglein 1 auto antibodies.[34,35]

Pemphigus vegetans:

Pemphigus vegetans is a rare variant of pemphigus vulgaris which is characterized by vegetating erosions, primarily in flexures. Two subtypes are recognized; the severe Neumann type and the mild Hallopeau type.[36]

Pathogenesis: Antibodies react with the 130 kDa desmoglein 1 antigen and possibly other antigens in both types.[36-40] Antibodies in the Hallopeau type also react with desmocollins 1 and 2.[41] Complement fixation might be responsible for the marked cutaneous infiltration of neutrophils and eosinophils.[38]

Clinical features: In the Neumann type, vesicles and bullae rupture to form hypertrophic granulating erosions, which bleed easily. The lesions evolve into vegetating masses exuding serum and pus. Erosions at the edge of the lesions induce new vegetations. In the Hallopeau type, early lesions are characterised by pustules rather than vesicles which soon progress to vegetating plaques. Spontaneous remission is possible.[42]

Oral lesions are less frequent than in pemphigus vulgaris.[43] Usual presentation is marked by serpiginous ulcers mainly on the dorsum of the tongue and lips. Papillomatous proliferations may be seen on the angle of the lips. Hyperplastic masses on the tongue can give a cerebriform appearance.[5,44]

Microscopy: In the Neumann type, early changes are similar to pemphigus vulgaris. In the late stages, verrucous hyperplasia and villi formation will occur and the acantholytic cells are inconspicuous. Suprabasal clefts filled with numerous eosinophils and degenerated acantholytic epidermal cells are seen in Hallopeau type, which becomes identical to the Neumann type in late stages. Eosinophilic pustules and microabscesses are seen.[1,43]

Direct immunofluorescence study: This demonstrates intercellular IgG sometimes with C3. Circulating intercellular antibodies can be detected in most patients by indirect immunofluorescence.[45]

Pemphius foliaceous:

Pemphigus foliaceus is less common worldwide than pemphigus vulgaris and in most parts of the world, probably accounts for only 10–20% of cases of pemphigus.[46-48] It occurs in both sporadic and endemic forms (Brazil).[47]

Pathogenesis: Autoantibodies directed against desmoglein-1, a 160-kDa desmosomal cadherin and certain drugs containing thiol groups like captopril, penicillamine etc. have been implicated to interfere with the function of desmosomes in the upper epidermis where desmoglein 3, which compensates for the loss of desmoglein 1 in the lower epidermis, is relatively sparse. This results in subcorneal separation. These antibodies stimulate epidermal cells to secrete plasminogen activator which results in increased plasminogen resulting in acantholysis.[49]

Clinical features: Lesions are seen mainly involving the 'seborrhoeic' areas like scalp, face, chest and upper back. Scaly lesions predominate as blisters are transient and rarely seen due to the very superficial level of the cleavage, leading to rapid rupture of the vesicles.

The scales separate leaving well-demarcated, crusted erosions surrounded by erythema.[45]

Oral lesions are uncommon as the desmoglein 3, which is distributed throughout the entire epithelium compensates for the loss of desmoglein 1. In the skin, desmoglein 3 is deficient at the subcorneal level where the loss of desmoglein 1 leads to subcorneal blister formation. Rarely superficial erosions can occur.[5]

Microscopy: Subcorneal bulla containing fibrin, some neutrophils and scattered acantholytic keratinocytes is seen. Epidermal eosinophilic spongiosis or neutrophilic spongiosis may precede the blisters. [50, 51]

Pemphigus erythematosus:

Pemphigus erythematosus is a variant of pemphigus foliaceus with immunological features of both lupus erythematosus and pemphigus.[52,53]

Clinical features: Erythematous, scaly lesions are seen over the nose and cheeks in a butterfly distribution simulating cutaneous lupus erythematosus or seborrhoeic dermatitis. Sunlight may exacerbate the disease. Oral mucosa is involved rarely. Superficial erosions may occur. This condition usually evolves into classical pemphigus foliaceus, sometimes to pemphigus vulgaris.[54]

Microscopy: Histology is not specific. Features are similar to pemphigus foliaceus.[54] Rarely interface dermatitis may also be present, making distinction from lupus erythematosus difficult.[1]

Direct immunofluorescence: Both granular IgG and C3 at the basement membrane zone and intercellular IgG and C3 in the epidermis are seen.[5,54]

IgA pemphigus:

This rare entity comprises a heterogeneous group clinically, histologically and immunologically. Two main subtypes are the subcorneal pustular type and the intraepidermal neutrophilic type.[5]

Pathogenesis: Auto-antibodies are directed against desmocollin-1, which is a desmosomal component located mainly in the upper epidermis, in case of subcorneal pustular type [55-56] and occasionally in the intraepidermal neutrophilic type.[55] In the intraepidermal neutrophilic type, antigens resembling desmogleins-1 or 3 have been implicated as the target antigens. [56,57] The pathogenic antibodies are of IgA variety which get deposited in the intercellular spaces of the epidermis.[58]

Clinical features: The disease mainly affects adults, though childhood cases have been reported.[59] Patients with both types have

flaccid vesicles or pustules arising on either erythematous or normal skin. The lesions may be pruritic and show a circinate or annular configuration with central clearance and evolve to crusted or scaly erythematous macules. The sites of predilection are the axillae and groins. Nikolsky's sign is usually negative. In some cases, the flaccid pustules resemble those seen in subcorneal pustular dermatosis. Mucous membrane involvement is very rare. Erosions or blisters can occur rarely. [60]

Microscopy: A neutrophil-rich polymorphonuclear infiltrate in the epidermis is seen. Subcorneal pustules are seen in the subcorneal pustular dermatosis type whereas intraepidermal pustules are seen in the intraepidermal neutrophilic type.[1] Acantholysis is usually sparse or absent.[53]

Direct immunoflourescence study: The hallmark of these disorders is intercellular IgA deposition at the upper level of epidermis in subcorneal type, at the lower or entire epidermis in intraepidermal type.[61] Circulating IgA is either undetectable or present in low titres.[60]

Paraneoplastic pemphigus:

Paraneoplastic pemphigus (PNP) was originally described by Anhalt et al. in 1990, a mucocutaneous disease associated with neoplasia,

most commonly B-cell lymphoproliferative disorders, thymoma, sarcomas and carcinomas.[62]

Pathogenesis: It is believed that the tumour antigens evoke a humoral autoimmune response. This immune reaction being directed against the neoplasm, provides protection against progression or dissemination of the tumour, but also cross-reacts with the host epithelial tissues, thus producing the mucocutaneous lesions. [62]

Clinical features: PNP consists of a polymorphous mucocutaneous eruption that overlaps with erythema multiforme and lichen planus pemphigoides including blisters, erosions, particularly on the upper body, and palmoplantar target lesion.[5] Involvement of the oral mucosa is the rule with the exception of thymoma associated paraneoplastic pemphigus. The mean age of onset is 60 years.[5] Paraneoplastic pemphigus has a poor prognosis with a mortality rate of around 90%. Successful treatment of the underlying malignancy results in remission of the associated pemphigus lesions.[63]

Microscopy: Histology depends upon the morphology of the lesion that is biopsied. Necrosis of keratinocytes or vacuolar interface dermatitis or suprabasal clefting with acantholysis is seen.[1, 64]

Direct immunoflourescence study: IgG deposits in the epithelial intercellular spaces and granular deposition of complement along the basement membrane zone is seen.[1,65]

Indirect immunofluorescence is positive in both non-stratifying (simple and transitional) and stratifying epithelia. Antibodies are predominantly antiplakin antibodies of the IgG1 subclass. [65]

Bullous pemphigoid:

Bullous pemphigoid is the most common type among the subepidermal bullous disorders.

Pathogenesis: IgG autoantibodies directed against two antigens: BPAg1 (BP230), an intracellular component of the hemidesmosome; BPAg2 (BP180, type XVII collagen) a transmembranous protein with a collagenous extracellular domain, bind to the basement membrane in patients with bullous pemphigoid. The binding of these antibodies at the basement membrane activates complement (C3) and inflammatory mediators which lead to subepidermal cleavage.[66,67]

Clinical features: Bullous pemphigoid mainly affects elderly people, with onset usually after 60 years of age.[68] Women are affected more (M:F – 1 to 1.7).[69] It commonly starts with itching and a non-

specific rash on the limbs that may be either urticaria-like or eczematous. The pruritus may persist for many months. The urticarial prodrome usually lasts 1–3 weeks before blisters occur while eczematous prodrome may precede the blisters by several months. Blisters are tense, dome shaped and appear mainly on the flexural aspects of limbs and on the central abdomen.[5,70]

Oral manifestations occur in 40% of cases and follow cutaneous eruptions. Generally bullous pemphigoid is characterised by smaller, slow growing and less painful oral lesions.[66,67] Because of the thick nature of the blister roof, intact vesicles and bullae can be seen in the oral cavity affecting the buccal mucosa, palate, gingival, tongue and lower lip. Gingiva can be affected in 16% resulting in desquamative gingivitis.[69]

Microscopy: Histopathology shows subepidermal bulla with the bulla cavity containing fibrin and eosinophils along with a dermal neutrophilic and eosinophilic infiltrate.[71]

Direct immunofluorescence study: Direct immunofluorescence study will show linear C3 deposition with or without IgG along the basement membrane zone. Use of salt split skin will reveal the deposits in the epidermal side or roof of the blister.[5,71]

Vegetating cicatricial pemphigoid (pemphigoid vegetans):

A rare subset of bullous pemphigoid that is clinically indistinguishable from pemphigus vegetans as it produces vegetating lesions and sometimes oral blisters and erosions. Direct immunofluorescence in this condition shows linear deposits of IgG and C3 at the epithelial basement membrane zone on oral biopsy, but there are no circulating anti-basement membrane antibodies.[72,73] Palate and gingiva are mainly involved.[74]

Epidermolysis Bullosa Acquisita:

EBA is a chronic blistering disease that can affect the skin and the oral mucosa. The circulating autoantibodies against collagen VII react to a dermal protein, which is a constituent of anchoring fibrils. The anchoring fibrils anchor the epidermis and its underlying basement membrane zone to the papillary dermis, whose function is lost due to these antibodies.[75]

Clinical features: There is no race or sex predilection. It occurs primarily in adults, although it also has been described in children and may occur in any age group.[76]

The classic form of EBA is characterized by fragility of the skin, blisters that coalesce and break open, and vesicles or bullae with localized skin erosions. Lesions heal with milia and scarring. The exposed skin areas such as knees, elbows, nails, feet, and hands are most often the target areas for injury. Loss of hair, nails, and esophageal involvement has been described.[77]

Microscopy: The histological findings depend upon the stage of the disease. The blister is seen at the subepidermal level. In the inflammatory type of the disease, there is a heavy predominantly neutrophilic infiltrate in the dermis whereas in the mechanobullous non-inflammatory phase, the infiltrate is usually sparse or absent.[78]

Direct immunofluorescence: Linear IgG deposits at the basement-membrane zone is found in all patients. Linear IgA and IgM may also be seen.[79] C3 has been reported in most cases. The basement membrane staining may be broader than that seen in bullous pemphigoid. A diagnostic U-serrated pattern has been described.[79] In salt split skin, deposits are seen on the dermal side.[80]

Immune electron microscopy shows IgG and C3 in the sublamina densa zone of the epithelial basement membrane.[81]

Mucous membrane pemphigoid (MMP):

MMP is an autoimmune vesiculobullous disease of the mucosal tissues and, rarely, the skin. It usually affects adults over 40 years of age and occasionally children. Only 10 cases of childhood MMP affecting the oral mucosa have been reported in the literature.[82] MMP occurs twice as often in women as in men, and no racial predilection exists.

Two types of skin lesion may occur, the most common of which is a generalized bullous eruption mimicking bullous pemphigoid. The second type is a localized one with erythematous plaques situated mainly over the extremities over which recurrent blistering occurs, with subsequent scarring and hyperpigmentation.[83]

Oral mucosal surfaces are the most frequently affected sites, predominantly the gingiva, where it presents as desquamative gingivitis. MMP may result in scar formation in other mucosal sites such as the conjunctiva but oral scarring is rare.[84]

It is a benign disease but can become life-threatening if laryngeal or oro-esophageal involvement occurs leading to stenosis. Progressive ocular lesions may result in entropion and blindness.[85,86]

Microscopy : Subepidermal bulla with an intact basal layer on the roof with minimal inflammatory infiltrate is seen in the dermis.[87] Lamellar fibrosis is present beneath the epidermis. In the mucosal surfaces, a lichenoid infiltrate is seen. [1]

Direct immunofluorescence study: This shows linear deposition of IgG, C3 and rarely IgA along the basement membrane.[88]

Dermatitis herpetiformis:

Dermatitis herpetiformis (DH) is a rare, intensely pruritic, chronic, recurrent, papulovesicular disease.

Pathogenesis: There is a strong association with HLA DR3 and HLA DQw2.[89] There is an underlying gluten-sensitive enteropathy in all patients that may be asymptomatic. The exact mechanism by which gluten causes blisters in the skin is still unknown. Autoantibodies (IgA) and T-cell reactions to tissue transglutaminases, are related to the pathogenesis.[90] The tissue transglutaminases cleave the gliadin into antigenic peptides and this may contribute to their role in pathogenesis.[91] The IgA deposits have been shown to be chemoattractant to neutrophils and there is activation of complement pathway which leads to the tissue injury. [92]

Clinical features: It affects men slightly more frequently than women. In a majority of cases the onset is between the second and fourth decades of life.[93] However, it can appear in later years and even in childhood. A positive family history is seen in 10.5% of patients.[94]

The onset may be acute or gradual, and pruritus is usually the first and predominant symptom. Early lesions are erythematous papules, urticarial weals or groups of small vesicles which often excoriate rapidly. The vesicles are usually seen in groups situated over erythematous plaques. Rarely blisters of about 1–2 cm diameter can occur. The distribution of the lesions is characteristic, with involvement of extensor aspects of the limbs, especially the knees, elbows, buttocks and the natal cleft.[68]

Incidence of oral lesions varies in various studies[94] and is generally rare. Recurrent aphthous ulceration is the most common lesion of the oral mucosa in those patients with symptomatic gut disease, followed by cheilitis, glossitis and angular stomatitis that occur due to malnourishment. Various studies have reported papulovesicular lesions, ulcers and erosions which may be associated with pain or burning sensation. Enamel defects occur in DH patients similar to celiac disease.[95]

Microscopy: The lesional skin will show polymorphonuclear leucocyte microabscesses in the tips of the papillary dermis that are multiloculated. Initially neutrophils predominate, but as they enlarge, eosinophils become more conspicuous. Later, the microabscesses fuse to form unilocular abscess, subepithelial blisters and then, erosions.[1]

Direct immunofluorescence study: Granular deposits of IgA along the basement membrane zone is seen in both lesional and non-lesional skin.[1]

Linear immunoglobulin A (IgA) Disease:

Linear IgA dermatosis (LAD) is an autoimmune subepidermal vesiculobullous disease that may be idiopathic or drug-induced. It can affect all ages from infants of few months age to the elderly (mean age of onset < 5 years and >60 years respectively), with no sex predilection. The childhood variety is said to be common in South Asian countries and has been historically referred to as chronic bullous dermatosis of childhood.[96,97]

Pathophysiology: IgA antibodies directed at a number of different target antigens, seem to be the underlying pathogenesis. The major antigen is BP180/collagen XVII and its shed ectodomain, LAD1 with molecular weights of 97 and 120 kDa. Other antigens include BP230,

LAD285, rarely collagen VII, the anchoring fibril component. In cases where type VII collagen is the target antigen against which the antibody response is directed, patients are less likely to be responsive to treatment.[98]

Clinical features: In children, the lesions comprise urticated plaques and papules, and annular, polycyclic lesions often with blistering around the edge, called as “the string of pearls” sign. Remission has been reported to occur in 64% of children, in most cases within 2 years. Disease of adults is more protracted with a mean duration of 5.6 years, lasting anywhere from 1-15 years. The blisters may arise from normal skin or from urticated plaques and can be haemorrhagic. The characteristic annular lesions with blisters around the edges are less common. The remission rate in adults is less than that in children (48%).[99]

Approximately in 80% of patients mucosal lesions can be observed (oral, ocular, nasal or genital mucosa). Almost 60 – 70 % of LAD patients have oral mucosal lesions. The most frequent oral lesions are painful erosive or ulcerative lesions caused by the rupture of bullae. These ulcerative or erosive lesions may appear anywhere in the oral mucosa, including vestibular mucosa and the tongue. [99]

Microscopy: The histological features are not specific for the condition. The subepidermal vesicles may contain numerous eosinophils suggestive of pemphigoid. In some blisters, neutrophils predominate and dermal capillary microabscesses are seen, suggesting dermatitis herpetiformis. Others show subepidermal blisters with non-specific features.[71]

Direct Immunofluorescence study: Linear deposition of IgA along the basement membrane zone is seen. There may also be other immunoreactants, IgG, IgM or C3. In salt split skin, the deposition of the autoantibodies is in the epidermal or dermal aspect or both.[100]

Bullous lichen planus:

Lichen planus is a common disease with worldwide distribution. The incidence of oral lichen planus varies from 0.5-2%.[101] About 30-70% of patients with skin lesions have oral involvement, while 15% present with only oral involvement.[102] Exact aetiology is unknown and it is a disease of multifactorial origin which includes genetic predisposition, viral infection, various drugs, dental amalgam filling, etc. [102]

A familial form, inherited as an autosomal dominant trait affects extremities in childhood and adolescent age group. Lichen planus pemphigoides is a condition where Lichen planus, a T-cell mediated

condition and Bullous pemphigoid, a humoral mediated disease coexist, affecting the skin and the oral mucosa. [103]

Distinct clinical subtypes such as reticular, plaque, erosive, atrophic and bullous types are recognised. Of these, the reticular type is the commonest while bullous variety is the rarest with only few cases reported till date.[2]

Bullae are often seen in the buccal mucosa and appear as flattened gelatinous plaques surrounded by a zone of erythema. Whitish reticulate lesions and striae can be found adjacent to the bullae or other intra oral locations. Symptoms include mild pain or burning discomfort.[2]

Histopathology: A subepidermal bulla with lichenoid infiltrate is seen.[5] In the oral mucosa, a subepithelial separation with the roof of the bulla composed of disoriented fragmented basal cells. The floor shows few fragmented basal cells overlying fibrous tissue with a zonal lymphocyte infiltrate. The margins blend with the adjacent mucosa that shows the typical changes of classical lichen planus as basal cell degeneration.[2]

Direct Immunofluorescence study: Deposition of fibrinogen in a fringe pattern along the basement membrane is the consistent finding.[2] Occasionally, IgM, IgG and C3 may be seen.[1]

Bullous lupus erythematosus:

Blistering eruptions are rare cutaneous manifestations of lupus erythematosus (LE) that may be caused by different mechanisms. Subepidermal clefting with frank vesiculation may occur in early lesions of acute, subacute and chronic cutaneous LE due to a severe vacuolar degeneration of the dermoepidermal junction. These vesiculobullous lesions are considered to be LE-specific.[104]

Pemphigus, bullous pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, and linear IgA bullous dermatosis have all been reported in association with LE. These blistering eruptions are considered to be non-specific for LE.[105]

Bullous SLE is a separate subset, with distinct clinical and histopathological features. The target antigen for the IgG and IgA auto-antibodies is type VII collagen, but other unknown antigens may also be involved in bulla formation.[105] Rarely drugs like hydralazine and IFN α may precipitate bullous SLE.[106,107]

Clinical features: The bullous lesions are predominantly seen on the face, neck and upper trunk, but may be more widespread, and may heal with milia formation. In Subacute cutaneous LE, erythema-

multiforme (EM)-like lesions can occur, a condition described as Rowell's syndrome. One third of the patients present with oral lesions.[108]

Microscopy: Histologically, the bullae are subepidermal with a neutrophilic infiltrate, occasionally resulting in microabscesses resembling dermatitis herpetiformis.[109]

Direct Immunofluorescence study: DIF studies show a linear deposition of IgA, IgG and IgM and to a lesser extent, C3 at the basement membrane, resembling bullous pemphigoid.[110]

Other findings: Electron microscopy shows the immunoreactants to be in the sublamina densa in contrast to pemphigoid, where it is seen in the lamina lucida. [110]

Erythema Multiforme (EM):

Erythema Multiforme is a hypersensitivity reaction usually triggered by infections, most commonly herpes simplex virus. Many different virus infections have been reported to trigger EM including Mycoplasma pneumonia, Parapoxvirus, Varicella zoster virus, Adenovirus, Hepatitis viruses, Human immunodeficiency virus (HIV), Cytomegalovirus and various viral vaccines. Many drugs have been reported to trigger EM including barbiturates, sulphonamides,

phenothiazines, penicillins, anticonvulsants and non steroidal anti inflammatory drugs.[111,112]

Clinical features: In erythema multiforme minor, mucous membrane involvement is mild or even absent. Erythema over the lips and buccal mucosa is the commonest manifestation. Sometimes blisters develop and quickly break to form erosions and ulcers. In EM major, one or more mucous membranes are typically affected. Most often the oral mucosa is involved (95-100%), most commonly lips, buccal mucosa and tongue, less commonly floor of the mouth, palate and gums.[113]

Lesions may remain stationary or slowly enlarge over several weeks or months (persistent erythema multiforme).[114,115]

Mucosal lesions range from tender superficial erythematous and hyperkeratotic plaques to painful deep hemorrhagic bullae and erosions. The blisters break quickly to leave large, shallow, irregular shaped, painful ulcers that are covered by a whitish pseudomembrane. Typically the lips are swollen with haemorrhagic crusts. The patient may have difficulty in speaking or swallowing due to pain. Oral EM is a distinct variety that manifests as chronic and recurrent lesions in the oral cavity alone. The diagnosis of this condition is by exclusion.[116]

Other mucosal sites that may get affected include eye, anus, genitals, respiratory tract and gastrointestinal tract. With mycoplasma pneumonia, the mucous membranes may be the only affected sites.[117]

Diagnosis: An etiology of herpes simplex virus can be established by evaluating the following criteria: recurrent EM, history of recurrent herpes, recent clinical herpes (preceding EM by 3 weeks) and demonstration of a recent HSV infection (seroconversion). Drug involvement is possible when there is a chronological relationship between the drug use and the eruption.[118,119]

Microscopy: The histology of EM is characteristic but not diagnostic. It varies with the age of the lesion and its clinical appearance.[120] Vacuolization of the basal cell layer, infiltrate of lymphocytes along the dermo-epidermal junction and a sparse, superficial, perivascular lymphoid infiltrate are seen in early stages[1]. The bullous lesions and desquamating lesions show subepithelial separation with numerous necrotic keratinocytes surrounded by lymphocytes (satellite cell necrosis). Immunostaining is not specific.[120]

In the drug induced variety, keratinocyte necrosis, microscopic blister formation, and pigmentary incontinenc are more. In those

associated with herpes simplex virus infection, there is more exocytosis, liquefaction degeneration of the basal layer and papillary dermal edema.[1]

Stevens-Johnson syndrome (SJS):

Stevens-Johnson syndrome and Toxic epidermal necrolysis appear to be the the same disease that vary in the severity based on body surface area involvement (<10- SJS; 10-30%- SJS TEN overlap; >30%- TEN). Various drugs have been implicated in their pathogenesis, mainly sulphonamides, beta lactam antibiotics, analgesics and non steroidal anti inflammatory agents(NSAIDs).[121]

The skin eruptions are preceded by a prodrome of high fever, malaise, arthralgia and myalgia lasting for 1-13 days. Extensive target lesions, blisters and erosions occur. Oral mucosa is involved in 100% of the cases,[122] showing extensive bulla formation, erosions and a greyish white membrane leading to the characteristic hemorrhagic crusting of the lips and the mouth. Other mucosa like eyes, genital and anal mucosa are also involved. Mortality rate ranges from 5-15% due to infection, toxaemia and renal damage. [123]

Microscopy: Histopathology is similar to erythema multiforme with necrosis of keratinocytes and dermal infiltrate.[123] Necrotic keratinocytes are more numerous involving full thickness of the

epidermis and subepidermal bulla is seen. The infiltrate is sparse in toxic epidermal necrolysis compared to erythema multiforme.[1]

Toxic epidermal necrolysis:

Toxic epidermal necrolysis is a rare clinicopathological entity with a high mortality rate (30-40%). An increased incidence of the disease in patients with HIV/Acquired immunodeficiency syndrome (AIDS) has been recorded.[124]

A prodromal illness precedes mucocutaneous manifestations by 1-2 days (1 day – 3 weeks). Entire skin surface and oral mucosa may be involved. Early skin lesions include macules with purpuric and blistering centre, urticarial or erythema multiforme which rapidly progresses to confluent erythema, followed by blistering and sloughing of large areas of skin in sheets. Nikolsky's sign may be positive.[125]

Oral lesions are seen in 95% of patients. They may precede the skin lesions by a day or so and may persist.[126] Gingival lesions are common and clinically are inflamed, with blister formation leading to painful, widespread erosions. Conjunctiva, cornea, iris and genital mucosa are severely affected.[127]

Microscopy: Early changes include epidermal spongiosis, exocytosis and moderate perivascular infiltrate. Later, necrosis of the whole epithelium which gets detached from the underlying lamina propria is seen.[127]

Other findings include anemia, leucopenia, thrombocytopenia, increase in aminotransferase levels, interstitial edema in chest X-rays are seen.[128]

Fixed drug eruption:

Fixed drug eruption (FDE) is a distinct drug induced reaction pattern that characteristically recurs at the same skin or the mucosal site. The pathogenetic mechanism underlying FDE is still enigmatic. The most commonly accepted hypothesis is persistence of memory T cells in the affected skin which is evident as increased ICAM-1 expression in the lesional skin. CD8+ cells phenotypically resembling effector memory T cells have been shown to be greatly enhanced in the lesions of FDE. [129]

The drugs that commonly cause mucosal FDE include co-trimoxazole, oxyphenbutazone, and tetracycline.[130]

The lesions of FDE usually start as an erythematous macule that subsequently evolves into a plaque. Vesicles and bullae develop at a later

stage and are usually hemorrhagic. The lesions can occur on any part of the skin and mucous membranes. The sites of predilection are the limbs, sacral region, genitalia, palmar and plantar skin.[131]

The oral mucosa may be involved in association with skin lesions or alone. Classically the transitional epithelium of the mucocutaneous junctions is involved. Systemic manifestations are uncommon and include fever, malaise, nausea, diarrhoea, abdominal pain, urethritis, and conjunctivitis. [131]

Microscopy: The histological changes are similar to erythema multiforme and toxic epidermal necrolysis. Necrotic keratinocytes with an eosinophilic cytoplasm and a pyknotic nucleus in the epidermis and pigment incontinence due to hydropic degeneration of the basal cell layer in the dermis are present.[1]

Aim of the Study

AIM OF THE STUDY

- To study the various acquired bullous dermatoses causing oral lesions
- To study the age distribution
- To study the sex distribution
- To study the intra oral distribution of lesions
- To study the evolution of the oral lesions with regard to the skin lesions in autoimmune bullous diseases

Materials and Methods

MATERIALS AND METHODS

Study design:

Single centred hospital based cross sectional study

Study period:

October 2009 to September 2011

Sample size:

Two hundred and fifty two patients

Data collection:

Proforma based

Inclusion criteria:

- Patients of acquired vesiculobullous disorders of all ages and both sex with active disease.

Exclusion criteria:

- Patients who have undergone treatment and those with inactive disease as evidenced by absence of lesions during the study period
- Patients who are unwilling to get included in the study

All patients with acquired vesiculobullous disorders who attended the out patient division of Dermatology department, Rajiv Gandhi Government General Hospital, Chennai from October 2009 to September 2011 were screened for oral lesions and detailed history was taken.

Patients were enquired regarding the onset, duration of the disease, the evolution of the lesions, whether the oral lesions preceded or followed or appeared at the same time with the skin lesions and any drug intake prior to the onset of the lesions. Precipitating or aggravating factors were noted. History of constitutional symptoms, loss of weight and appetite, melena, urticarial weals, pruritus, photosentivity, abdominal pain, diarrhoea, constipation, joint pain, symptoms of the oral lesions, previous similar episodes were noted. Other coexisting diseases if present, were documented.

Personal history regarding diet, other associated diseases and treatment history were noted. Family history of similar skin disease was taken.

All patients were subjected to routine clinical examination including general, systemic and dermatological examinations. The morphology and distribution of the lesions in the skin and oral cavity were recorded. Clinical signs (Nikolsky’s sign, bulla spreading sign) were

elicited in the respective patients. The extent of oral lesion in patients with pemphigus vulgaris was rated using 3 grades as follows: Grade I - Only 1 site is involved; Grade II - 2 sites are involved; Grade III - 3 or more sites are involved.

Investigations including Tzanck smear, routine blood parameters, urine examination, chest x-ray, etc were done. Biopsies (skin/ oral mucosal biopsy/ both) were done in appropriate patients. Patients with oral lesions in sites other than the lips, were taken to the Department of Oro maxillo facial surgery, Government Dental College and Hospital, Chennai for biopsy. Direct immunofluorescence study was done only in selected patients (patients with oral lesions alone, discordant skin & mucosal biopsy results) because of cost constraints and lack of feasibility. Serological confirmation was done only in patients with primary episodes of herpes simplex by HSV IgM Elisa technique. Viral culture in vero cell lines was done for the first 25 oral herpes simplex patients for confirmation. For the rest of the patients, serology and culture were not done due to lack of feasibility.

Observation and Results

OBSERVATION & RESULTS

Out of the total 87,429 patients who attended the dermatology OPD during the study period, 252 patients were acquired vesiculobullous dermatoses (0.29%). Among these, 126 were viral infections, 114 were autoimmune bullous dermatoses and 12 were drug induced. Of the total 252 patients, oral lesions were present in 175 patients (69.4%). Among the 126 patients with viral infections, 92 had oral lesions (73%). Among the autoimmune group, 72 out of 114 patients had oral lesions (63.2%). Of the 12 patients in the drug induced group, 11 had oral lesions (91.7%).

Table 1. AGE DISTRIBUTION OF THE TOTAL PATIENTS

Age	Viral	Autoimmune	Drug induced	Total	Percentage
<=20 years	24	2	3	29	11.5%
21-30 years	25	11	4	40	15.9%
31-40 years	28	25	3	56	22.2%
41-50 years	19	32	0	51	20.2%
51-60 years	14	16	2	32	12.7%
61-70 years	12	23	0	35	13.9%
>71 years	4	5	0	9	3.6%
Total	126	114	12	252	100%

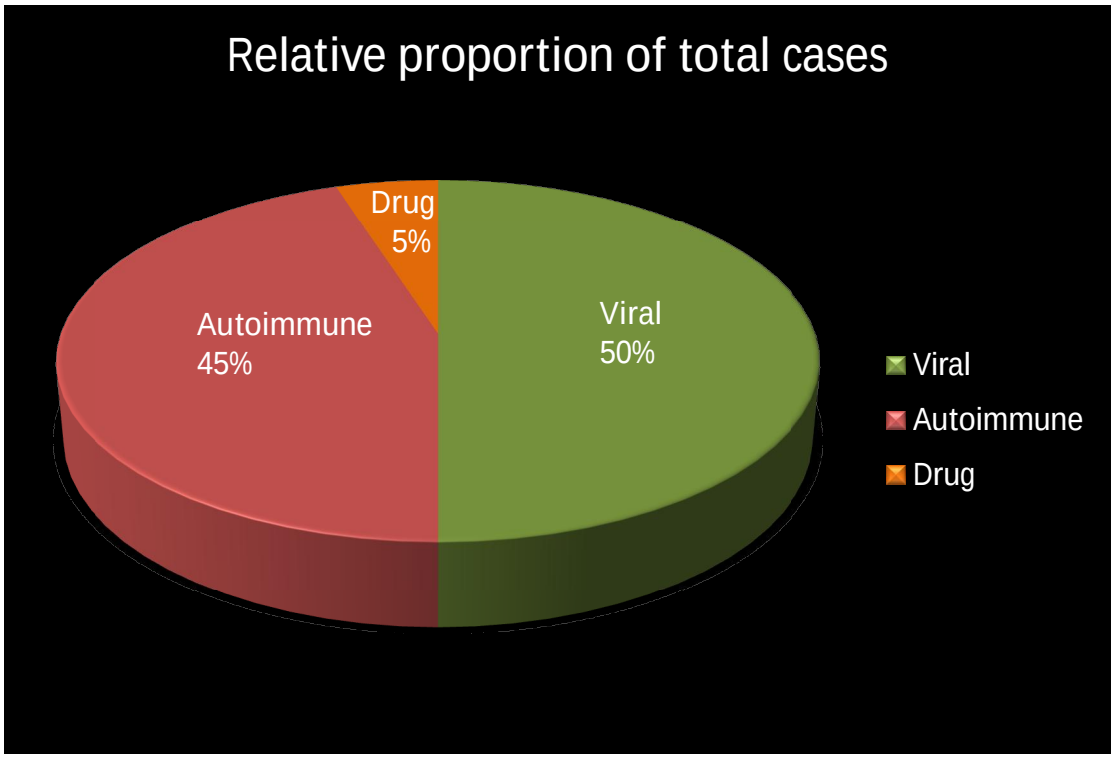
The age distribution varies from 2 years to 73 years (mean - 35.98) in the viral group, 17 to 85 years in the autoimmune group (mean - 47.18) and 16 to 60 years (mean - 31.58) in the drug induced group. In the first decade, viral infections were more common than the autoimmune dermatoses.

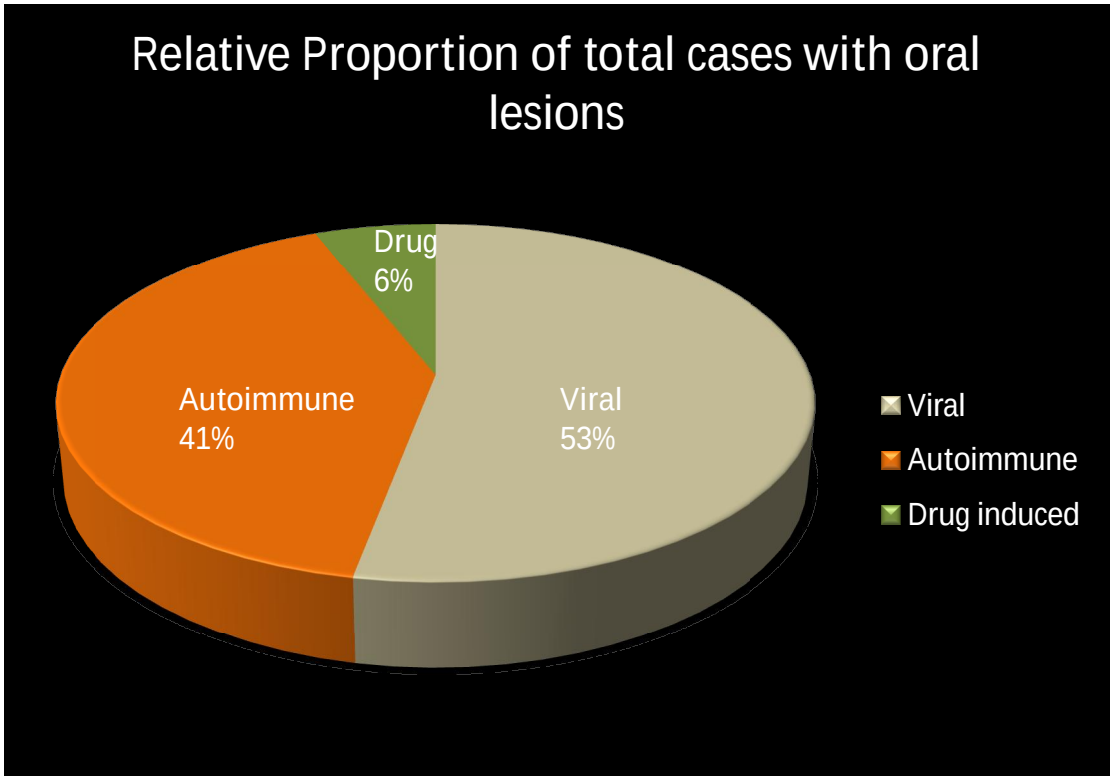
Sex distribution:

The gender wise distribution varies as given in the table 2. Overall, there were 148 females and 104 males (M:F- 1:1.4). Viral infections showed a male to female ratio of 1 : 1 (64:62) whereas in the autoimmune group, it was 1:4 (33:81). In the drug induced group, there was a slight male predominance (1.4 : 1) with 7 males and 5 females.

Table 2. SEX DISTRIBUTION OF THE TOTAL PATIENTS

Sex	Viral	Autoimmune	Drug induced	Total	Percentage
Male	64(50.8%)	33(28.9%)	7(58.3%)	104	41.3%
Female	62(49.2%)	81(71.1%)	5(41.7%)	148	58.7%
Total	126	114	12	252	100%


Relative proportion of total cases
Drug
5%
Autoimmune
45%
Viral
50%
Viral
Autoimmune
Drug


Relative Proportion of total cases with oral lesions
Drug
6%
Autoimmune
41%
Viral
53%
Viral
Autoimmune
Drug induced

VIRAL INFECTIONS (Table 3) :

. Viral infections constituted the major part of the acquired vesiculobullous dermatoses (50%). Various viral infections and their relative proportion are shown in the table 3. Herpes simplex was the most common viral infection constituting about 77.1% of the total patients followed by varicella zoster virus (19.8%) infection.

Table 3. Viral Infections.

		Oral lesions	No oral lesions	Total	Percentage
Herpes simplex		87	10	97	77.1%
Varicella zoster	Chicken pox	0	4	4	3.1%
	Herpes zoster	3	18	21	16.7%
Hand, foot and mouth disease		2	2	4	3.1%
Total		92	34	126	100%

Age distribution (Table 4):

Majority of the viral infections were seen in 4^{th} decade (21.4%) followed by 3^{rd} decade (19.8).

Table 4. Age distribution in viral infections:

Age (years)	Herpes simplex		Chicken pox		Herpes zoster		Hand, foot & mouth disease		Total	Percent
	Oral	No oral	Oral	No oral	Oral	No oral	Oral	No oral		
0-10	1	1	0	0	1	0	2	2	7	5.6%
11-20	17	0	0	2	0	0	0	0	19	15.1 %
21-30	23	1	0	1	0	0	0	0	25	19.8%
31-40	21	4	0	0	1	1	0	0	27	21.4%
41-50	14	3	0	0	0	4	0	0	21	15.1%
51-60	5	0	0	1	1	5	0	0	12	11.1%
>60	7	0	0	0	0	8	0	0	15	11.9%
Total	88	9	0	4	3	18	2	2	126	100%

Herpes simplex was seen in all age groups while herpes zoster was less common before the 3rd decade. Hand, foot & mouth disease was exclusively seen in the first decade.

Sex distribution (Table 5):

The total number of males was almost equal to that of females (64 : 62). The sex distribution was 1:1. There was no sex predilection as a whole as well as in any of the individual viral infection.

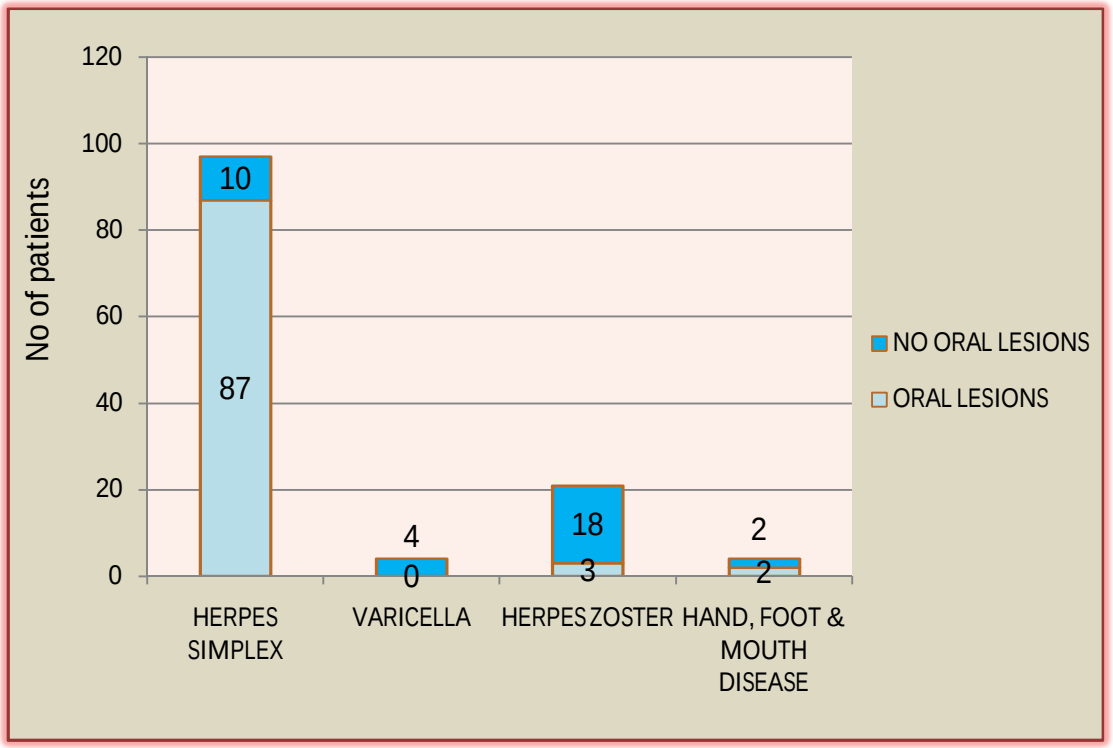
Table 5. Sex distribution in viral infections:

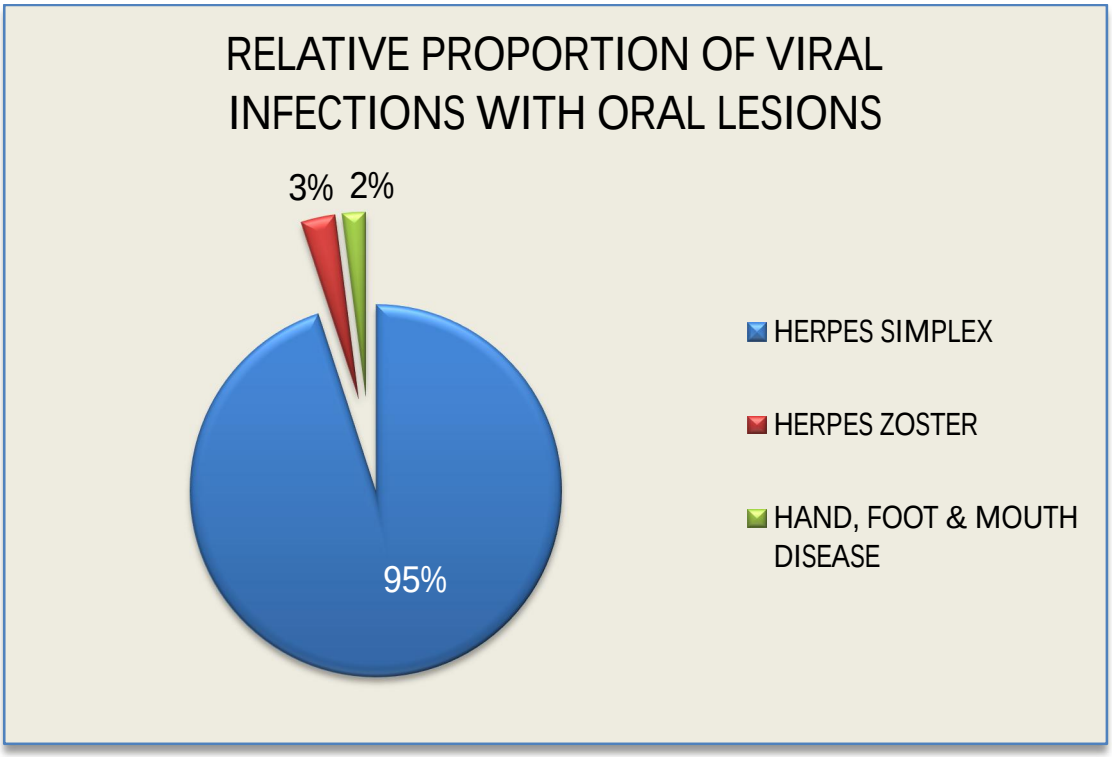
	Male		Female		Total
	Oral	**No oral lesions**	**Oral**	**No oral lesions**	
Herpes simplex	41	7	46	3	97
Chicken pox	0	3	0	1	4
Herpes zoster	2	9	1	9	21
Hand, foot &mouth disease	0	2	2	0	4
Total	43 (34.1%)	21 (16.7%)	49 (38.9%)	13 (10.3%)	126

Herpes simplex:

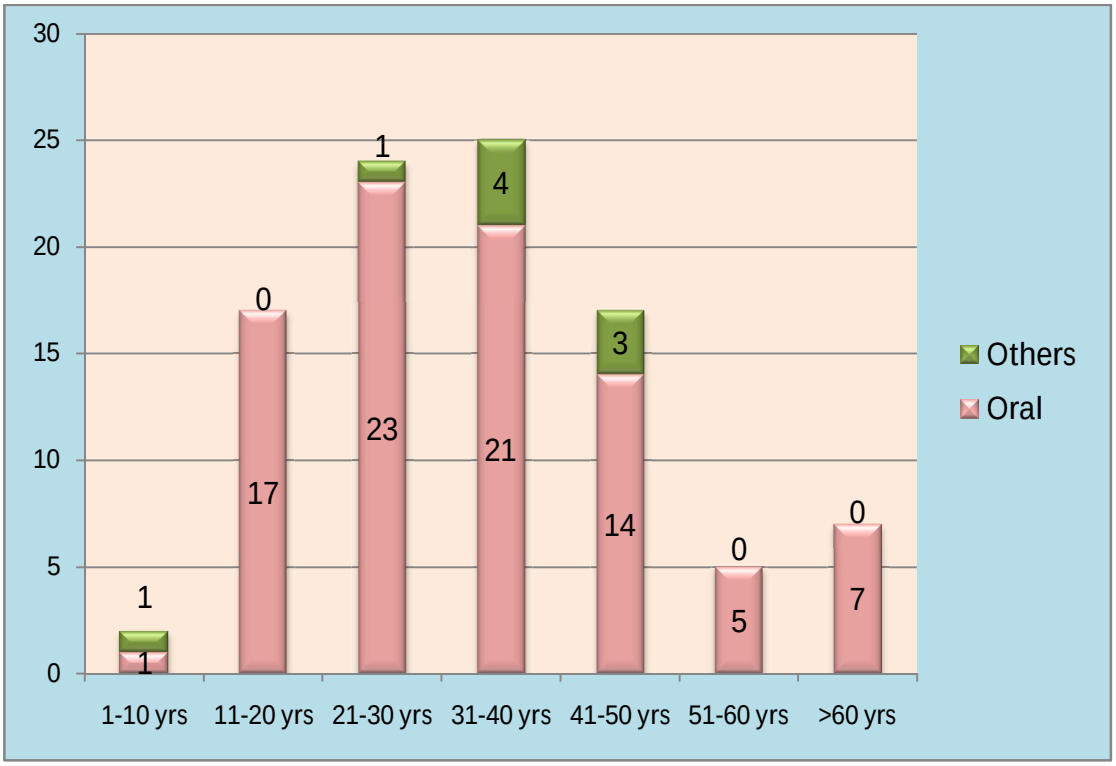
Among the 97 patients of herpes simplex, 87 patients had isolated oral involvement, 6 had isolated nasal mucosal involvement and 3 had isolated genital mucosal involvement. One patient had both nasal and oral mucosal involvement. Only 3 of the patients with oral lesions had primary episode (confirmed by culture and HSV IgM ELISA) while the rest of them had recurrent episodes. All the three primary episode patients were found to be positive for HSV 1 antibodies. Two patients had recurrent intraoral herpes simplex (RIOH) which were confirmed by culture.

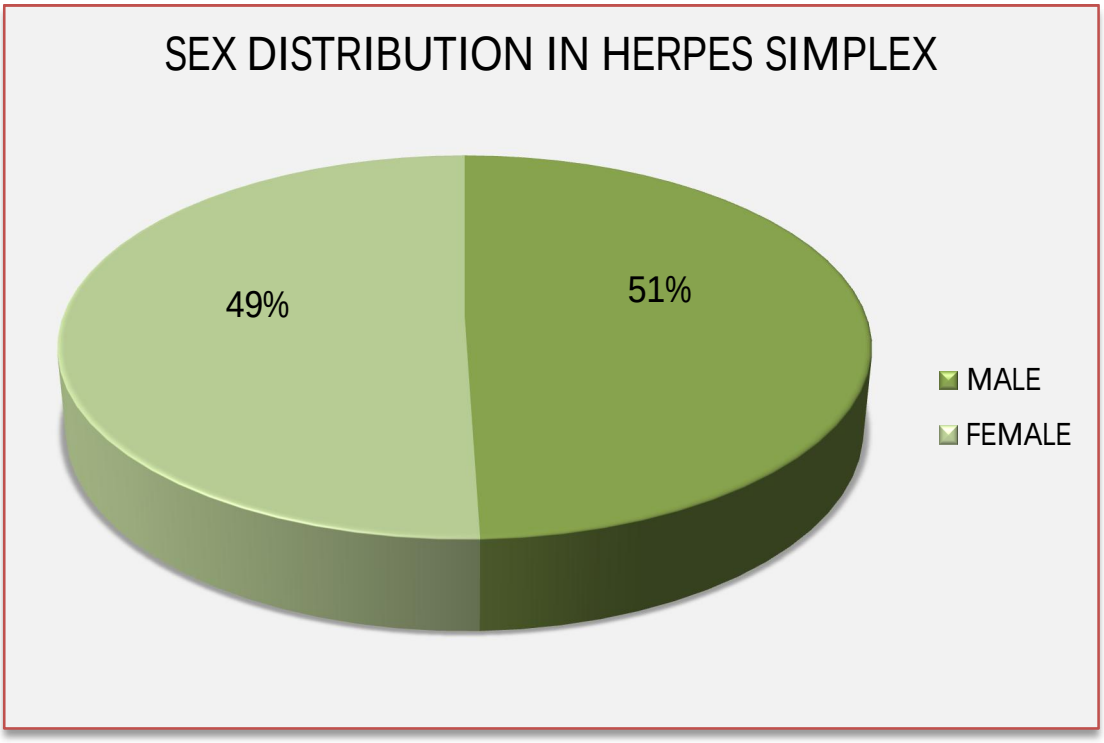
VIRAL INFECTIONS





AGE DISTRIBUTION OF HERPES SIMPLEX





Oral involvement:

Of the 87 patients with oral herpes, 3 were primary herpetic gingivostomatitis, 2 were recurrent intraoral herpes simplex and the rest of them (82) were recurrent herpes labialis. Lips were the predominant site affected, seen in 85 patients (97.7%). Tongue was involved in all the 3 primary herpetic gingivostomatitis and 2 recurrent intraoral herpes patients (5.7%). Palate was involved in 2 of the 5 patients with primary episode (2.3%). Gingiva was the least to get involved (1.1%). Meningitis was encountered in one case.

Chicken pox/ Varicella & Herpes zoster:

None of the four patients of Varicella had enanthem. Out of the 21 patients with herpes zoster, oral lesions were found in 3 of them (14.3%). Ramsay Hunt syndrome with lower motor neuron facial palsy and vesicles in the ipsilateral pinna & tongue was present in two patients and maxillary zoster involving left half of the palate and upper labial mucosa was seen in one patient.

Hand, foot and mouth disease:

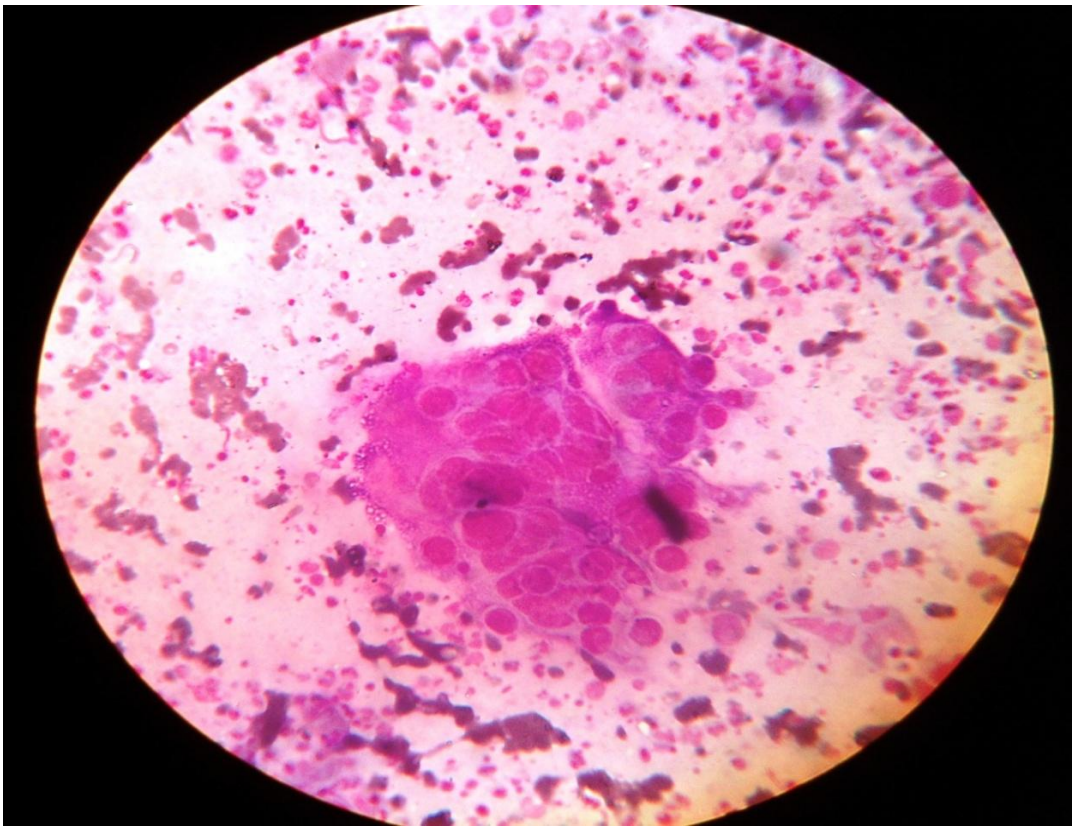
Of the 4 patients seen, two patients had oral lesions. Tongue was the site of involvement in one while lips were involved in the other.

PRIMARY HERPETIC GINGIVOSTOMATITIS

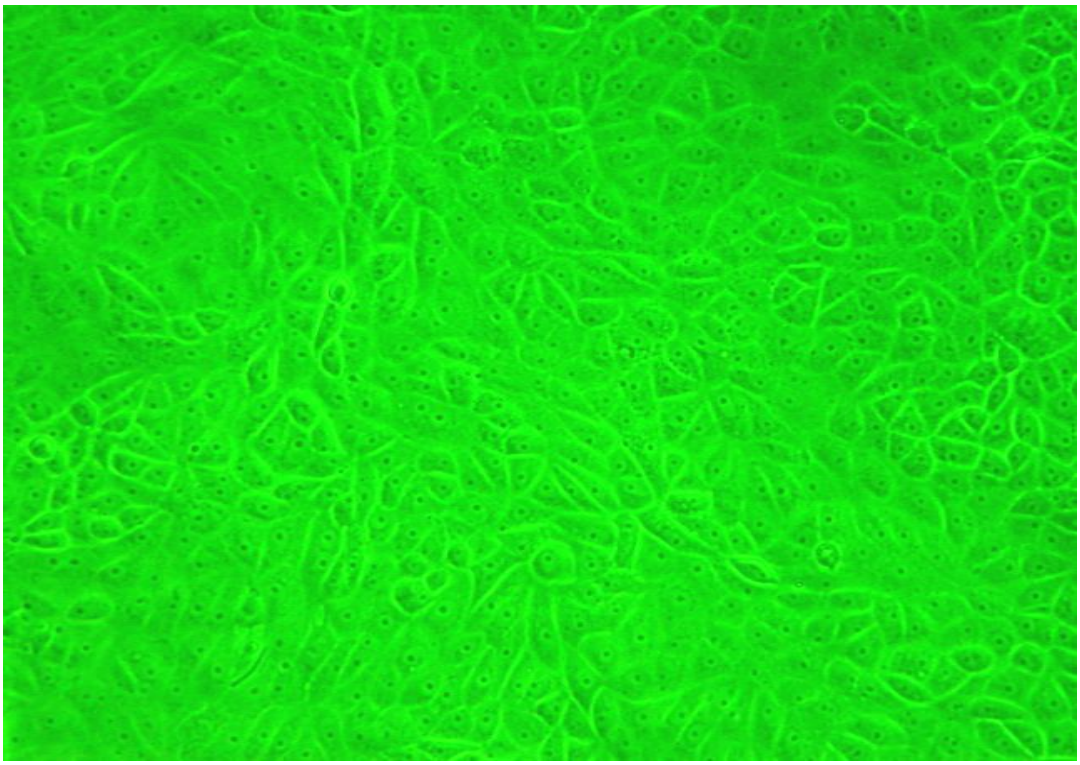
RECURRENT INTRAORAL HERPES SIMPLEX

RECURRENT HERPES LABIALIS WITH NASAL INVOLVEMENT

MULTINUCLEATED EPITHELIAL GIANT CELLS

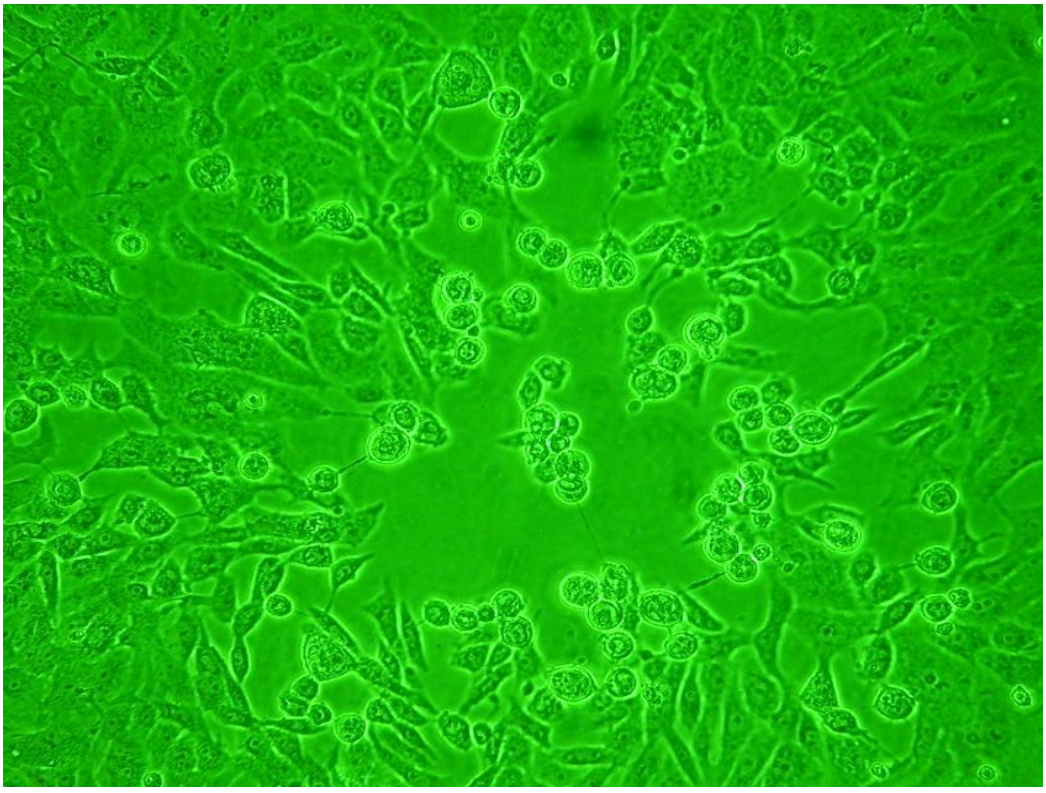


UNINFECTED VERO CELL LINES



HSV CULTURE – CYTOPATHIC EFFECTS

(MULTINUCLEATED CELLS)

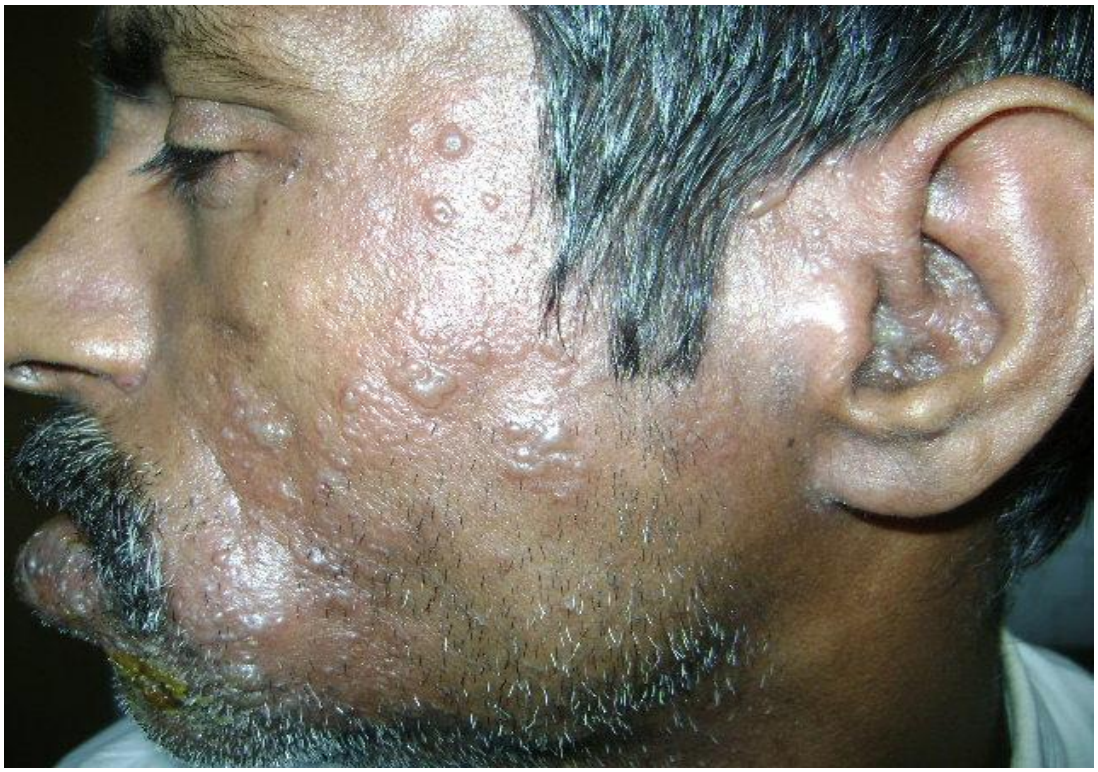


MAXILLARY HERPES ZOSTER INVOLVING THE LIPS

VESICLES AND EROSIONS IN THE PALATE IN MAXILLARY HERPES ZOSTER

RAMSAY HUNT SYNDROME

VESICLES IN THE PINNA AND CHEEK



VESICLES AND EROSIONS IN THE LIPS AND TONGUE WITH DEVIATION OF ANGLE OF MOUTH

RAMSAY HUNT SYNDROME - DEVIATION OF ANGLE OF THE MOUTH

HAND, FOOT AND MOUTH DISEASE

AUTOIMMUNE VESICULOBULLOUS DISORDERS:

Out of the 114 patients, pemphigus vulgaris was the most common dermatoses (59.7% of the total patients). Among the total of 114, 72 patients had oral mucosal involvement among which pemphigus vularis was most common (84.7%) followed by bullous pemphigoid (8.3%) (Table 6).

Table 6. **Autoimmune bullous disorders.**

	NUMBER OF PATIENTS		TOTAL
	WITH ORAL LESIONS	WITHOUT ORAL LESIONS	
Pemphigus vulgaris	61(84.7%)	7 (16.7%)	68 (59.7%)
Pemphigus vegetans	3 (4.2%)	0 (0%)	3 (2.6%)
Pemphigus foliaceous	0 (0%)	11 (26.2%)	11 (9.6%)
Pemphigus erythematosus	0 (0%)	6 (14.3%)	6 (5.3%)
Bullous pemphigoid	6 (8.3%)	16 (38.1%)	22 (19.3%)
Dermatitis herpetiformis	2 (2.8%)	2 (4.7%)	4 (3.5%)
Total	72 (63.2%)	42 (36.8%)	100%

Age distribution:

The age distribution of various autoimmune bullous disorders has been tabulated (Table 7).

The age distribution varies from 17 to 85 years (mean - 47.18). Pemphigus vulgaris was most commonly seen in 4th decade followed by 5th decade (mean - 43.45). Bullous pemphigoid was more common in the seventh followed by sixth decade ranging from 24 to 85 years (mean - 57.54). All the 3 patients with pemphigus vegetans were in the 5th decade.

Table 7: Age distribution in autoimmune bullous disorders:

Age in years		<=20	21-30	31-40	41-50	51-60	61-70	71-80	>80	Total
Pemphigus vulgaris	With oral	2	10	16	15	11	6	1	0	68
	Without oral	0	0	3	2	1	1	0	0	
Pemphigus vegetans	With oral	0	0	0	3	0	0	0	0	3
	Without oral	0	0	0	0	0	0	0	0	
Pemphigus foliaceous	With oral	0	0	0	0	0	0	0	0	11
	Without oral	0	0	3	5	2	0	1	0	
Pemphigus erythematosus	With oral	0	0	0	0	0	0	0	0	6
	Without oral	0	0	0	3	3	0	0	0	
Bullous pemphigoid	With oral	0	1	1	1	2	0	1	1	22
	Without oral	0	0	1	2	4	7	1	0	
Dermatitis herpetiformis	With oral	0	0	1	1	0	0	0	0	4
	Without oral	0	0	0	0	0	2	0	0	
Total		2	11	25	32	23	16	4	1	114

Sex distribution (Table 8):

The sex distribution in the autoimmune bullous dermatoses is tabulated. Overall, females were the most affected (M:F- 1 : 2.4). In

pemphigus vulgaris, the difference was more marked (M:F – 1: 3.9) whereas in bullous pemphigoid, it was less marked (M:F – 1 : 1.4). In pemphigus foliaceous (M:F – 1: 1.8) and pemphigus erythematosus (M:F – 1: 5), there was a predilection for females. Dermatitis herpetiformis was exclusively seen in males.

Table 8. SEX DISTRIBUTION IN THE AUTOIMMUNE GROUP

Disease	Male		Female		Total
	Oral lesions	No oral lesions	Oral lesions	No oral lesions	
Pemphigus vulgaris	13	1	48	6	68
Pemphigus vegetans	1	0	2	0	3
Pemphigus foliaceous	0	4	0	7	11
Pemphigus erythematosus	0	1	0	5	6
Bullous pemphigoid	2	7	4	9	22
Dermatitis herpetiformis	2	2	0	0	4
Total	18	15	54	27	114

Oral cavity involvement:

Oral lesions were seen in 61 out of the 68 patients of pemphigus vulgaris (89.7%) whereas in bullous pemphigoid, it was present in 6 out

of the 22 patients (27%). None of the pemphigus foliaceous and pemphigus erythematosus group had oral lesions. All the 3 pemphigus vegetans patients had oral lesions (100%). 2 out of the 4 dermatitis herpetiformis (50%) patients had oral lesions.

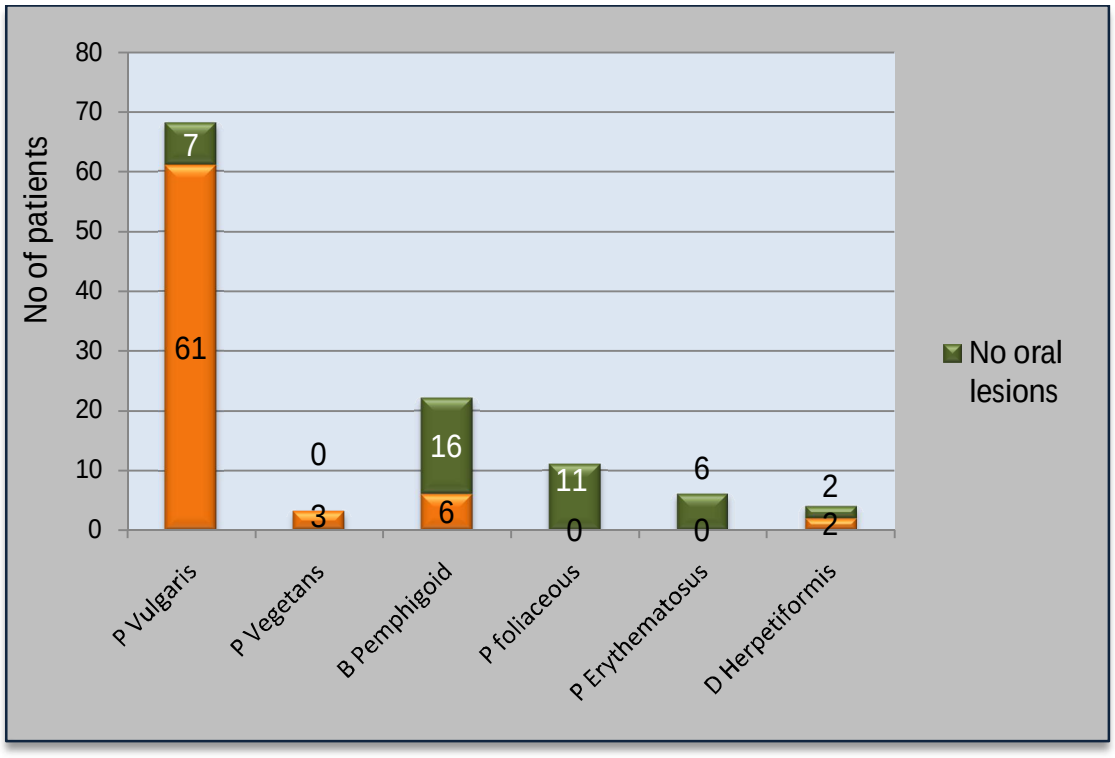
Site of involvement in the oral cavity:

Buccal mucosa (72%) was the most common site involved in pemphigus vulgaris followed by the labial mucosa (69%). In bullous pemphigoid, buccal mucosa (83.3%) followed by gingiva (50%) were the commonest sites involved. Among the total 6 patients, 3 had isolated buccal mucosal involvement, 2 had both gingival and buccal mucosal involvement and 1 patient presented with isolated desquamative gingivitis. Of the two DH patients with oral lesions, lips were involved in both while tongue was involved in one of them.

Morphology of oral lesions:

Erosions were predominant in the pemphigus vulgaris patients (93.4%). Intact vesicles/bullae were seen only in 4 patients (6.5%) whereas in bullous pemphigoid, intact bullae were seen in 3 out of the 6 patients (50%).

AUTOIMMUNE DISEASES



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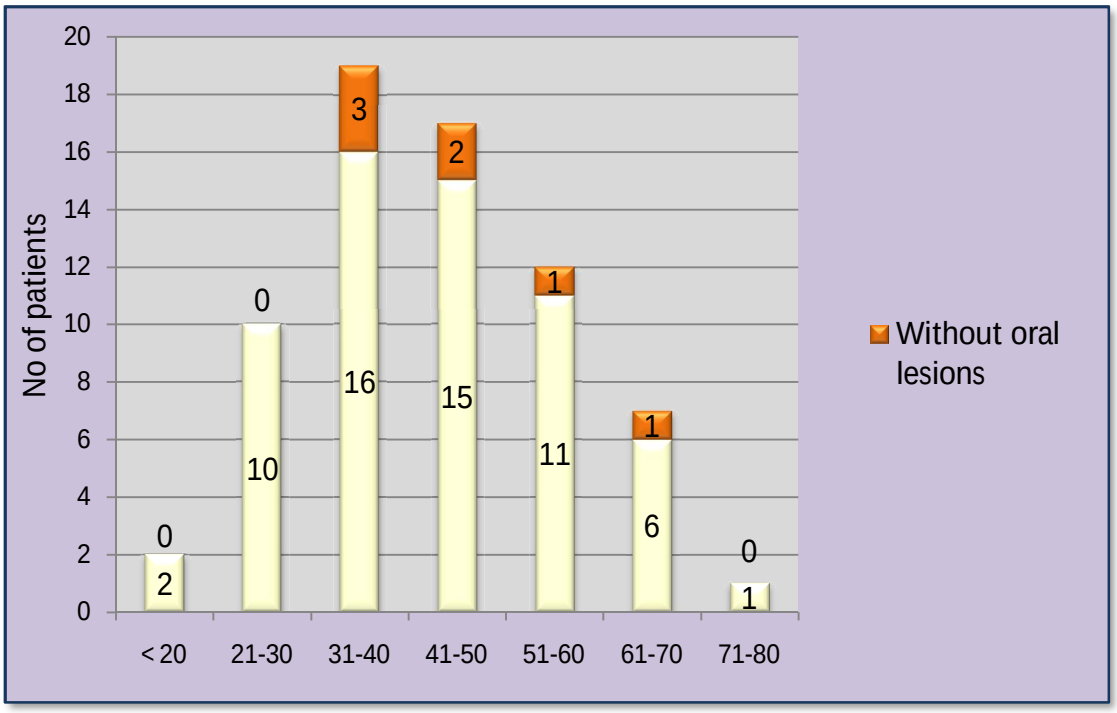
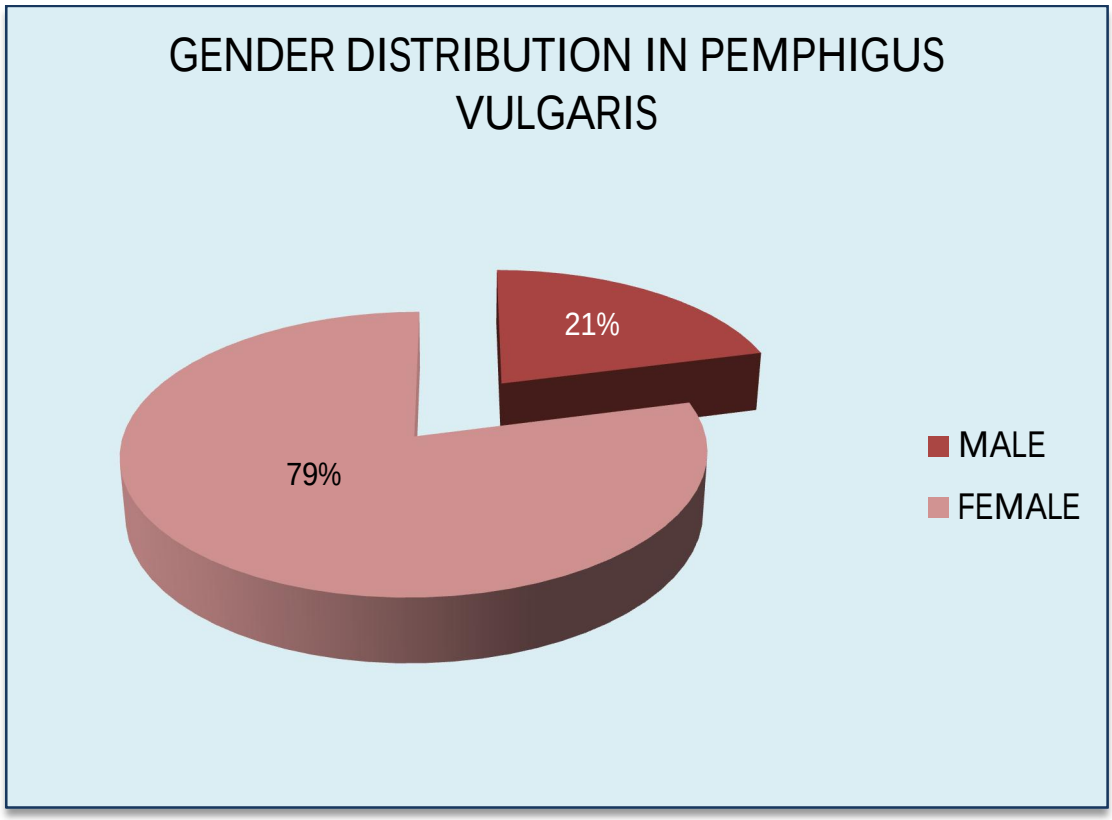
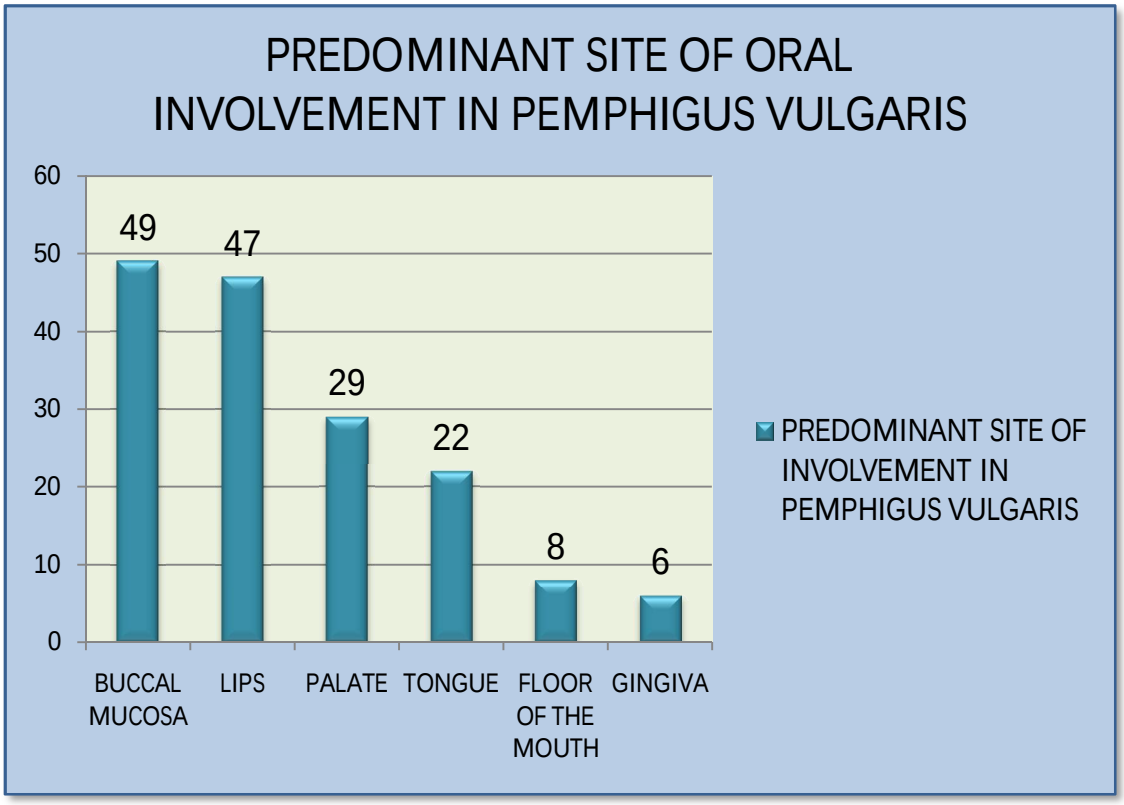
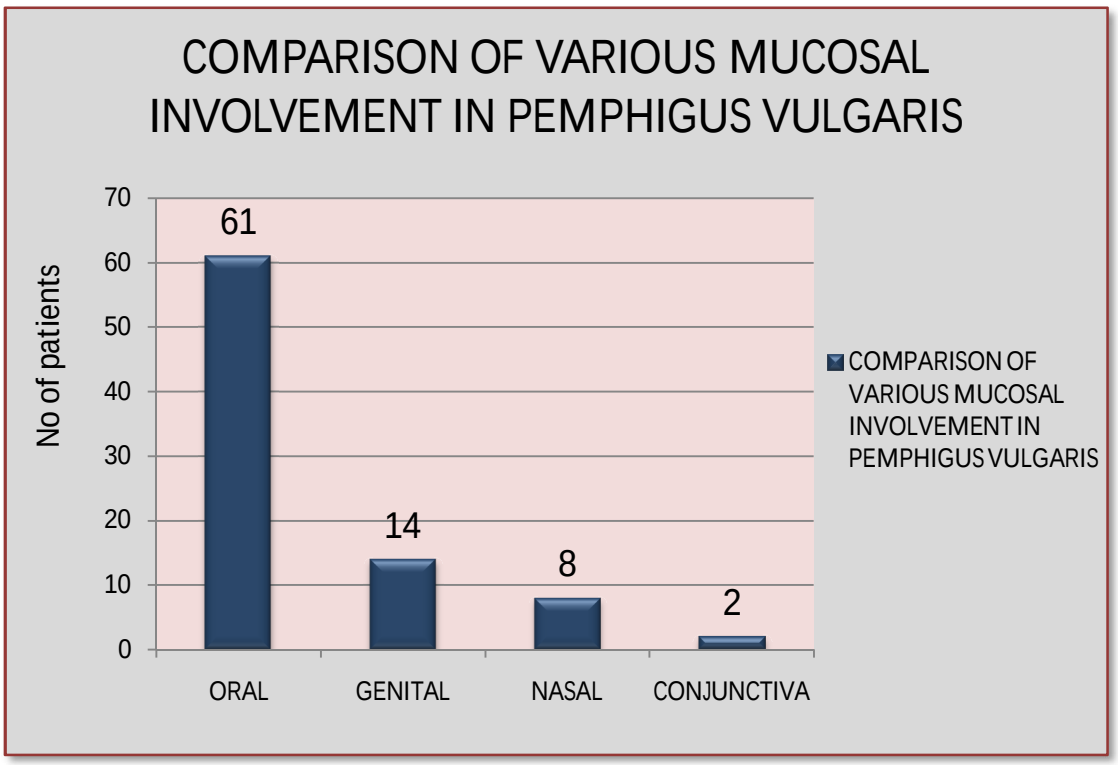
AGE DISTRIBUTION OF PEMPHIGUS VULGARIS

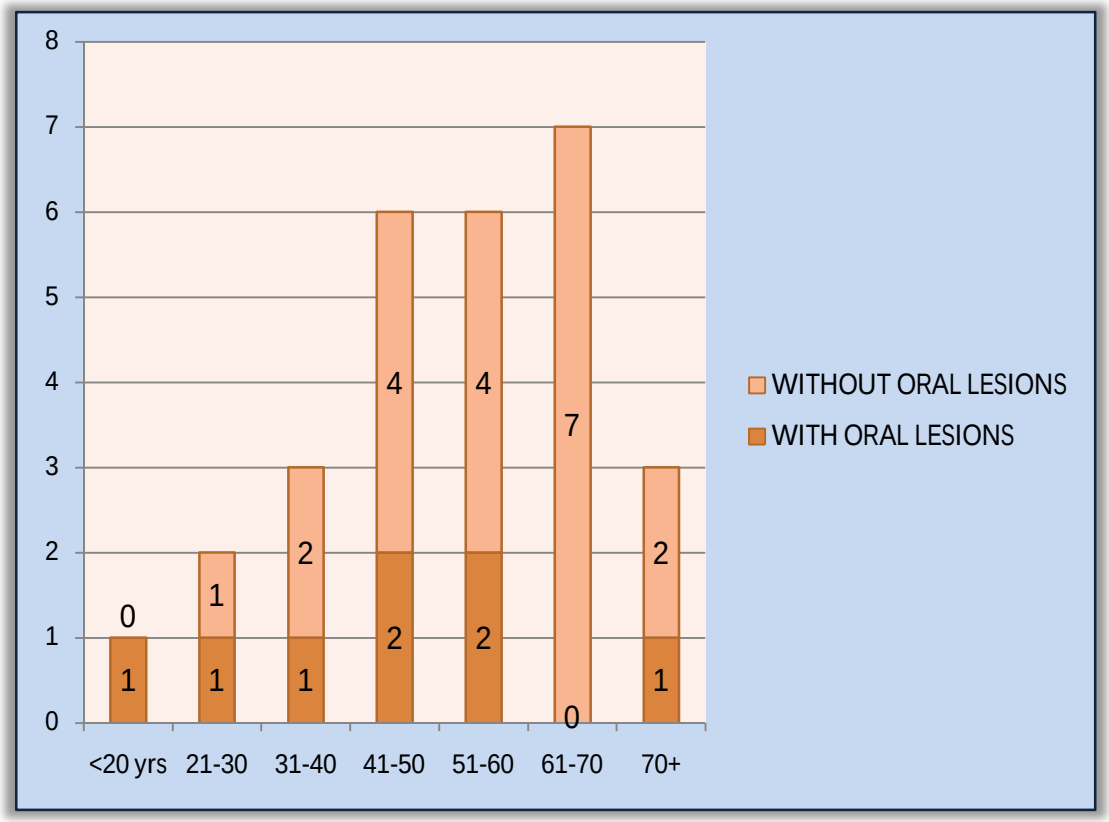



GENDER DISTRIBUTION IN PEMPHIGUS VULGARIS
21%
79%
MALE
FEMALE

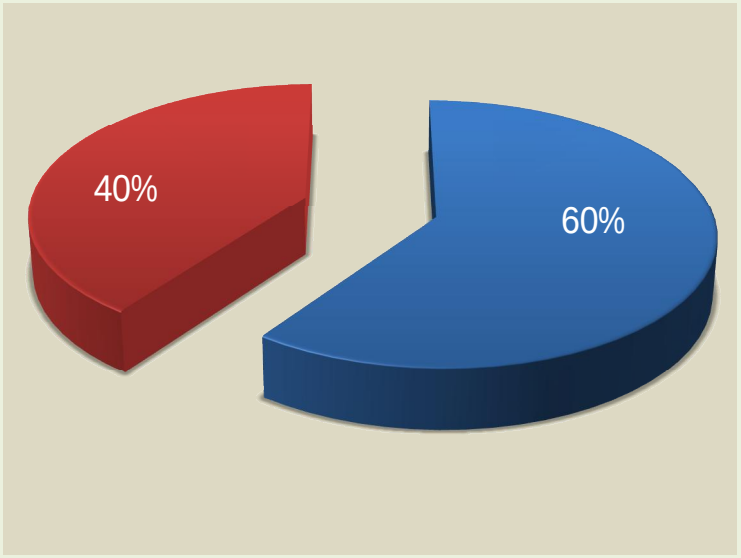

PREDOMINANT SITE OF ORAL INVOLVEMENT IN PEMPHIGUS VULGARIS
60
50
40
30
20
10
0
49
47
29
22
8
6
BUCCAL MUCOSA
LIPS
PALATE
TONGUE
FLOOR OF THE MOUTH
GINGIVA
PREDOMINANT SITE OF INVOLVEMENT IN PEMPHIGUS VULGARIS



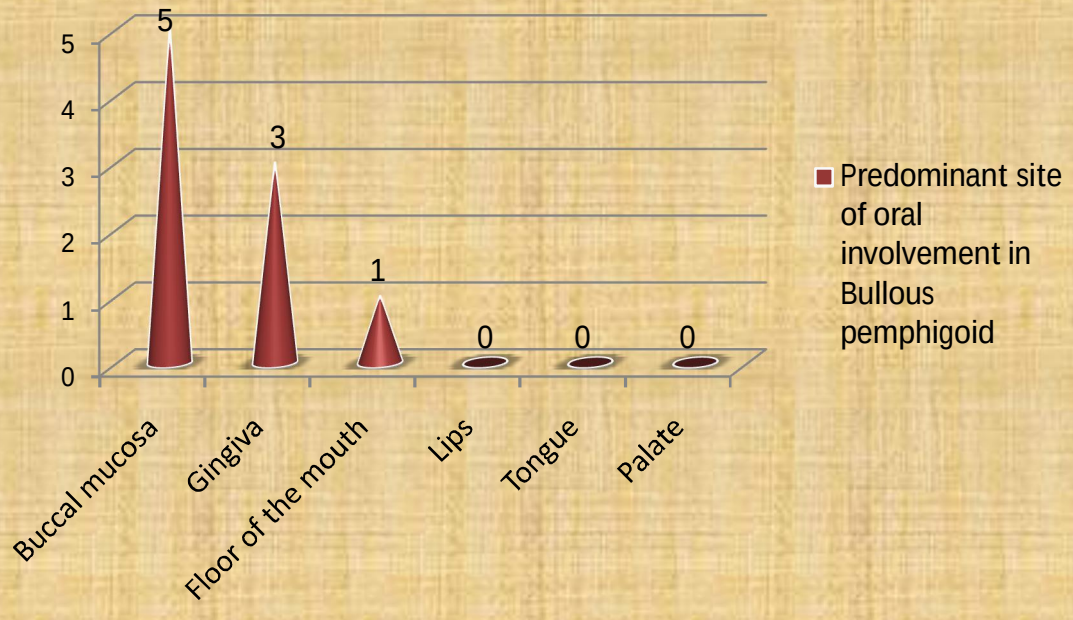
AGE DISTRIBUTION OF BULLOUS PEMPHIGOID



GENDER DISTRIBUTION IN BULLOUS PEMPHIGOID



Predominant site of oral involvement in Bullous pemphigoid



Initial site of involvement in the oral cavity:

Buccal mucosa was the most common site to get involved first in the oral cavity (44.3%) followed by lips (31.1%) and tongue (18%) in pemphigus vulgaris. Gingiva and buccal mucosa were the first to get affected in 50% each of the patients with bullous pemphigoid.

Table 9. Initial site of involvement in the oral cavity.

	Lips	**Buccal mucosa**	**Tongue**	**Palate**	**Gingiva**	**Pharynx**	**Total**
Pemphigus vulgaris	19	27	11	2	0	2	61
Pemphigus vegetans	1	2	0	0	0	0	3
Bullous pemphigoid	0	3	0	0	3	0	6
Dermatitis herpetiformis	2	0	0	0	0	0	2
Total	22	32	11	2	3	2	72

Extent of oral lesions:

Among the 61 patients with oral lesions, 35 patients (57.4%) had Grade III involvement of the oral cavity followed by Grade II involvement in 19 patients (31.1%) and Grade 1 in 7 patients (11.5%).

Onset of the lesions in skin and oral cavity (Table 10):

Of the 61 patients of pemphigus vulgaris with oral lesions, 8 patients had only oral lesions without skin involvement. Among the remaining 53 patients, oral involvement preceded the onset of skin lesions in 33 patients (62.3%) while skin involvement preceded the onset of oral lesions in 10 patients (18.7%) and in the remaining 10 patients (18.7%), both had simultaneous onset.

Table 10. Onset of the lesions in skin and oral cavity

	Simultaneous onset	**First involved oral**	**Average time interval before skin involvement**	**First involved skin**	**Average time interval before oral involvement**
Pemphigus vulgaris	10	33	36.6 days	10	145.7 days
Bullous pemphigoid	0	2	120 days	4	52.5 days
Pemphigus vegetans	1	2	14 days	0	-
Dermatitis herpetiformis	0	0	-	2	630 days
Total	11	14		37	

The average time interval between the onset of oral and skin involvement in those with first involvement in the oral cavity was 36.6 days whereas in those with first involvement in the skin was 145.6 days.

Among the 3 pemphigus vegetans patients, 2 patients had lesions in the oral cavity first and 1 had simultaneous onset of skin & oral lesions. Among the 6 patients with bullous pemphigoid, oral mucosa was first affected in 2 patients with an average time interval of 120 days.

Superinfection with candida (Table 11):

Of the total 61 patients of pemphigus vulgaris, 53 patients (86.9%) had candidal superinfection whereas none of the bullous pemphigoid, pemphigus vegetans and Dermatitis herpetiformis patients had candidiasis. This was a statistically significant association (P value – 0.0001).

Table 11 : Candidal superinfection

	Scraping for Candida		**Total**
	Positive	**Negative**	
Pemphigus vulgaris	53	8	61
Bullous pemphigoid	0	6	6
Pemphigus vegetans	0	3	3
Dermatitis herpetiformis	0	2	2

PEMPHIGUS VULGARIS - FLACCID VESICLES AND EROSIONS

PEMPHIGUS VULGARIS - FLACCID VESICLES AND EROSIONS

PEMPHIGUS VULGARIS - EROSIONS OVER LIPS

PEMPHIGUS VULGARIS -EROSIONS OVER BUCCAL MUCOSA

PEMPHIGUS VULGARIS -PALATAL EROSIONS

PEMPHIGUS VULGARIS - EROSIONS OVER FLOOR OF THE MOUTH

PEMPHIGUS VULGARIS - EROSIONS IN THE TONGUE

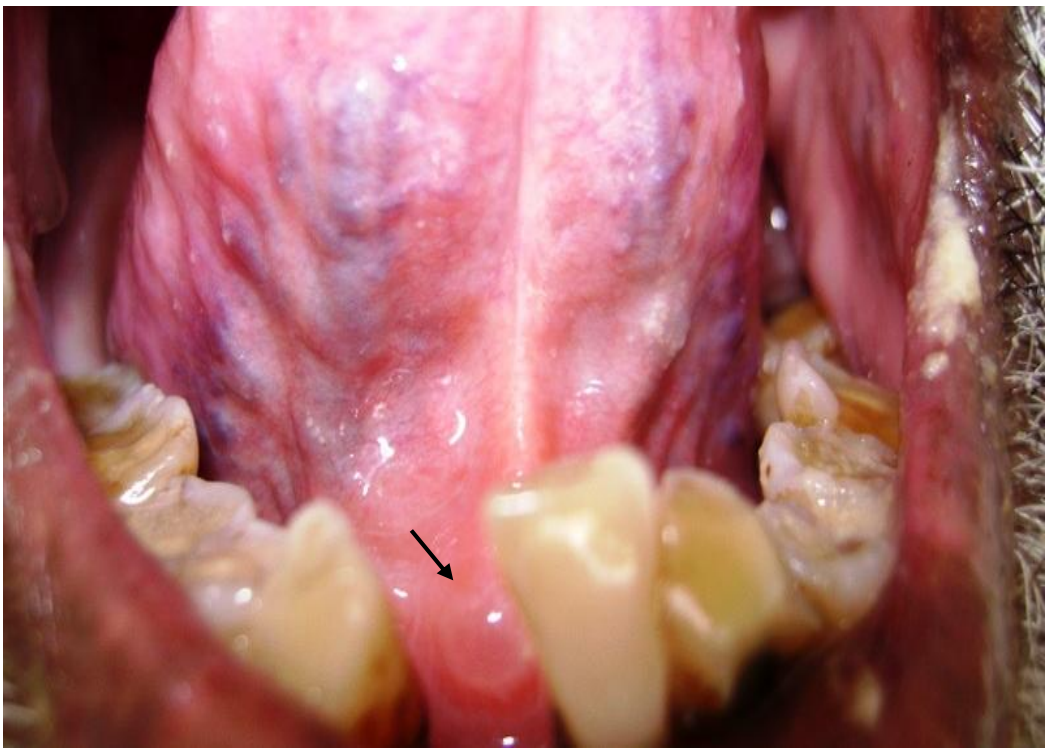
PEMPHIGUS VULGARIS - EROSIONS IN SUBLINGUAL MUCOSA

CONJUNCTIVAL INVOLVEMENT IN PEMPHIGUS VULGARIS

CEREBRIFORM TONGUE IN PEMPHIGUS VEGETANS

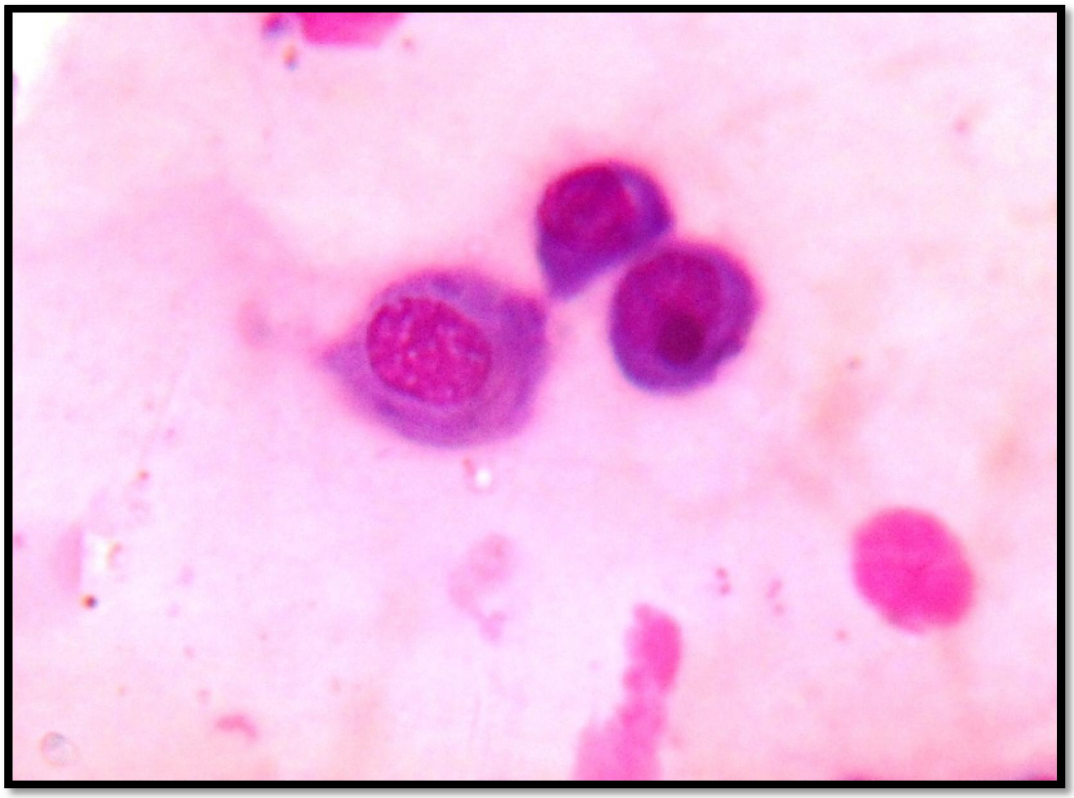
BULLOUS PEMPHIGOID - INTACT BULLA IN BUCCAL MUCOSA

INTACT BULLA IN BULLOUS PEMPHIGOID- SUBLINGUAL AREA

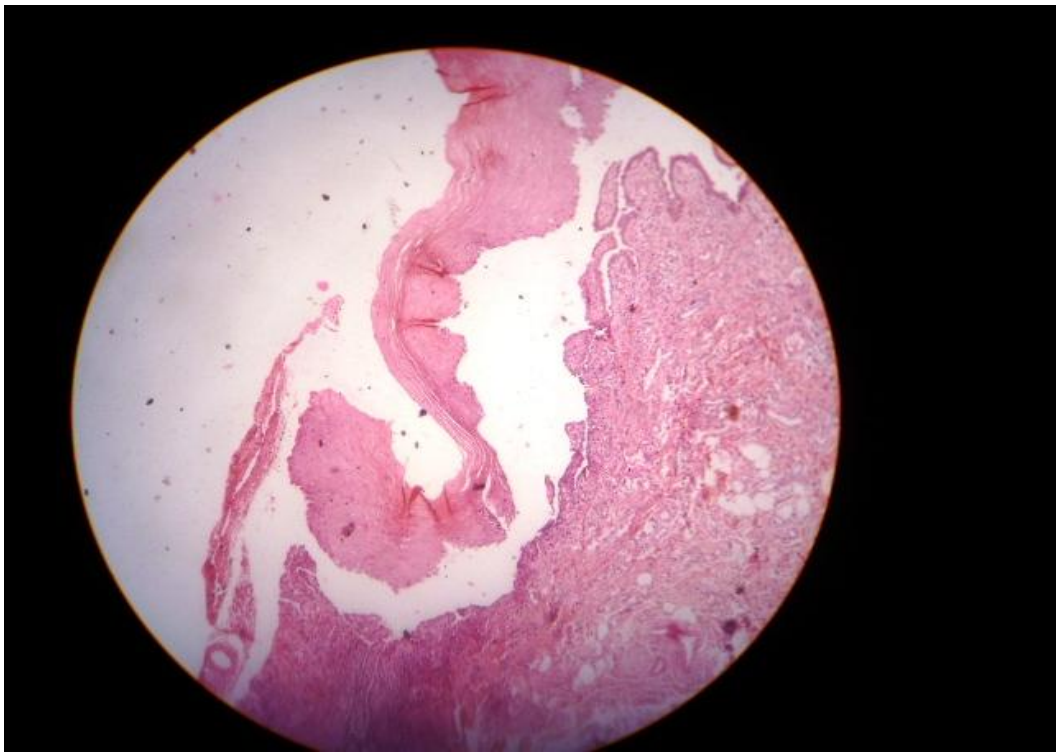


DESQUAMATIVE GINGIVITIS IN BULLOUS PEMPHIGOID

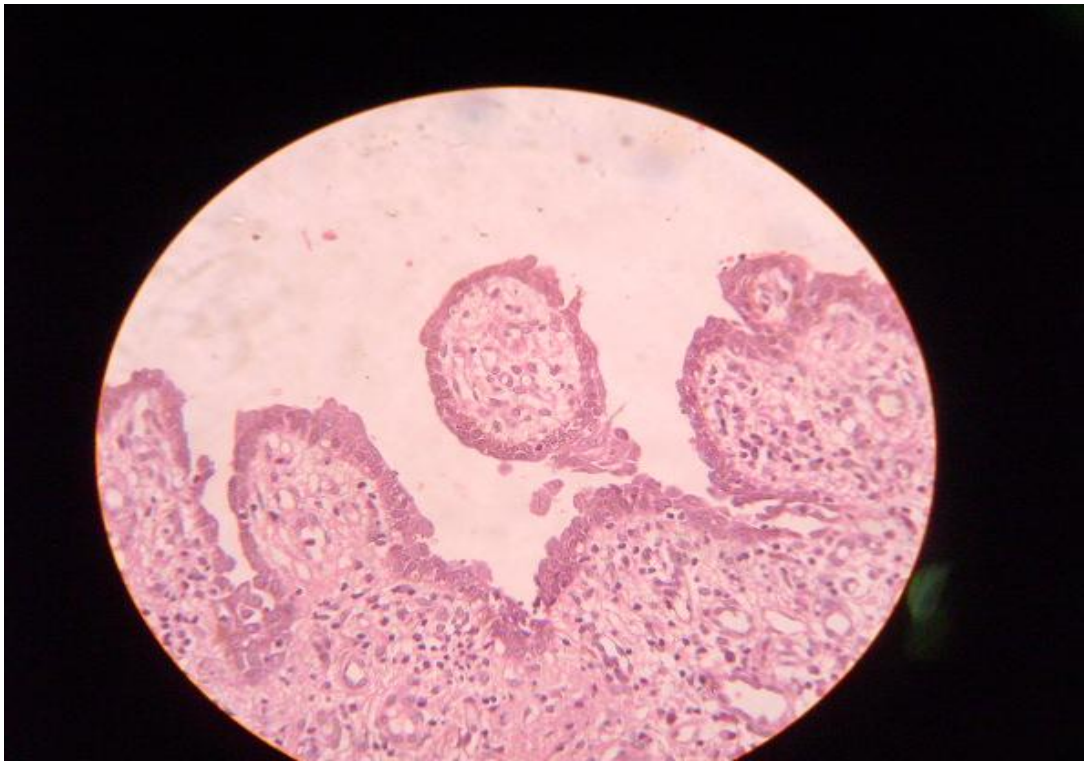
ACANTHOLYTIC CELLS OF PEMPHIGUS VULGARIS



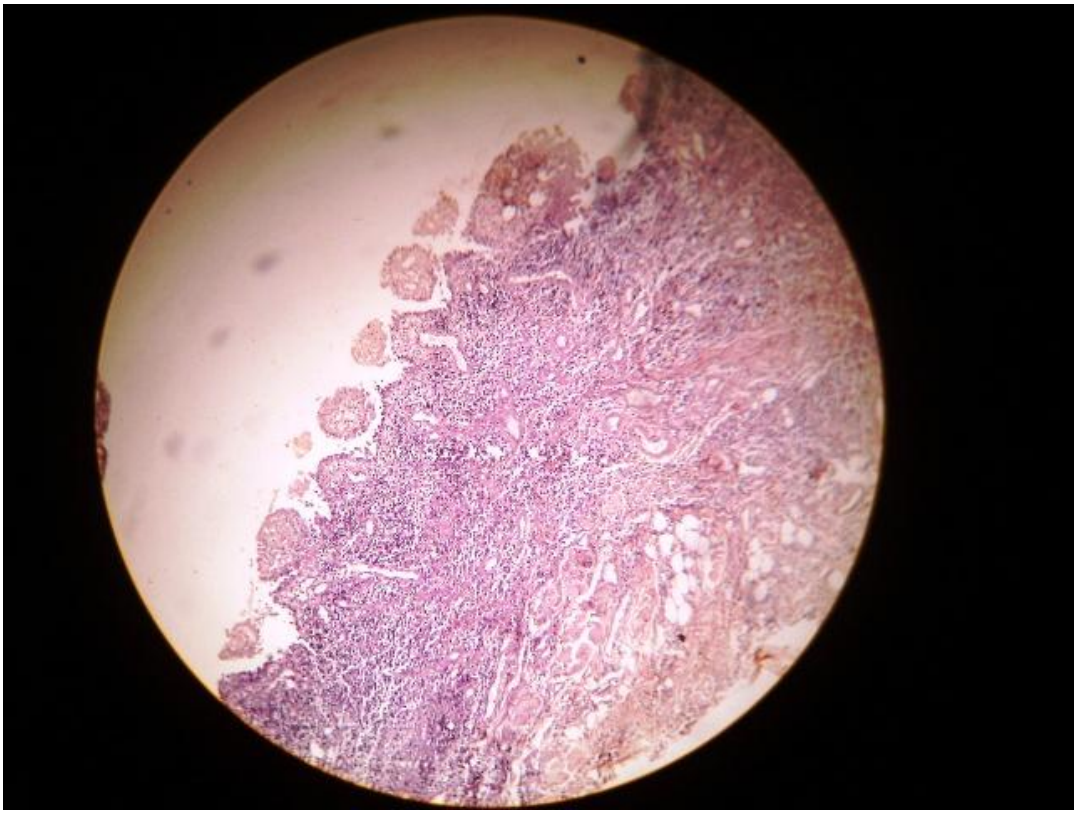
HPE- SUPRABASAL BULLA IN BUCCAL MUCOSA (10X)



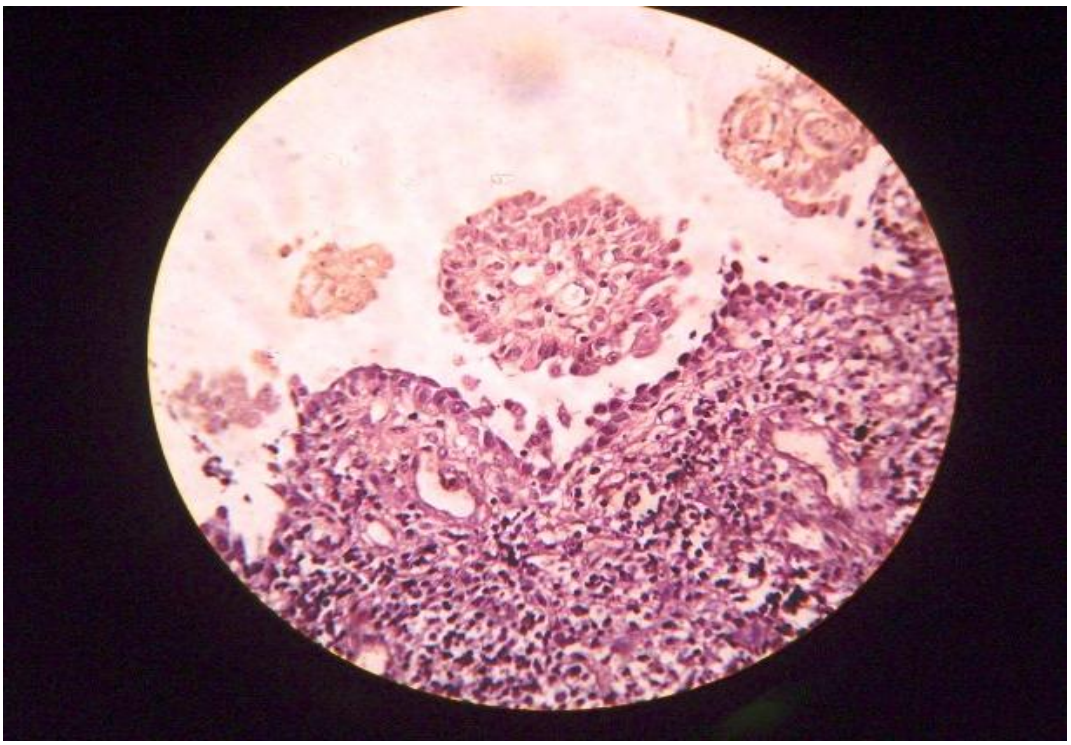
HPE- SUPRA BASAL BULLA (40X)



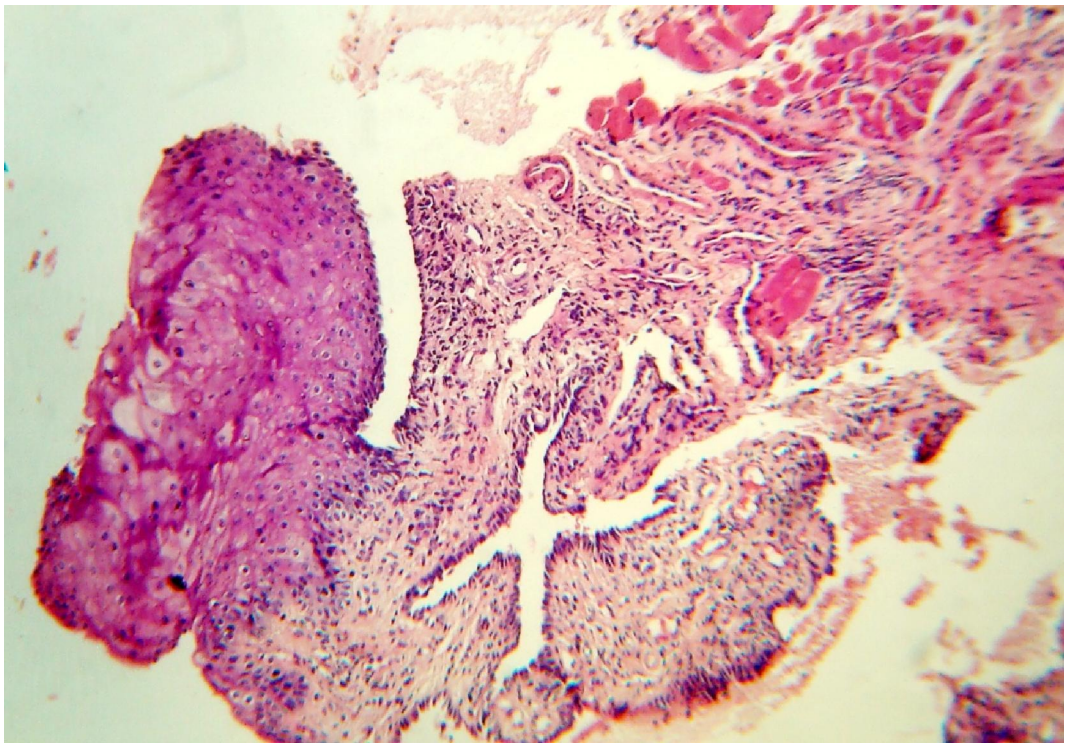
HPE- SUPRABASAL SEPARATION IN LABIAL MUCOSA (10X)



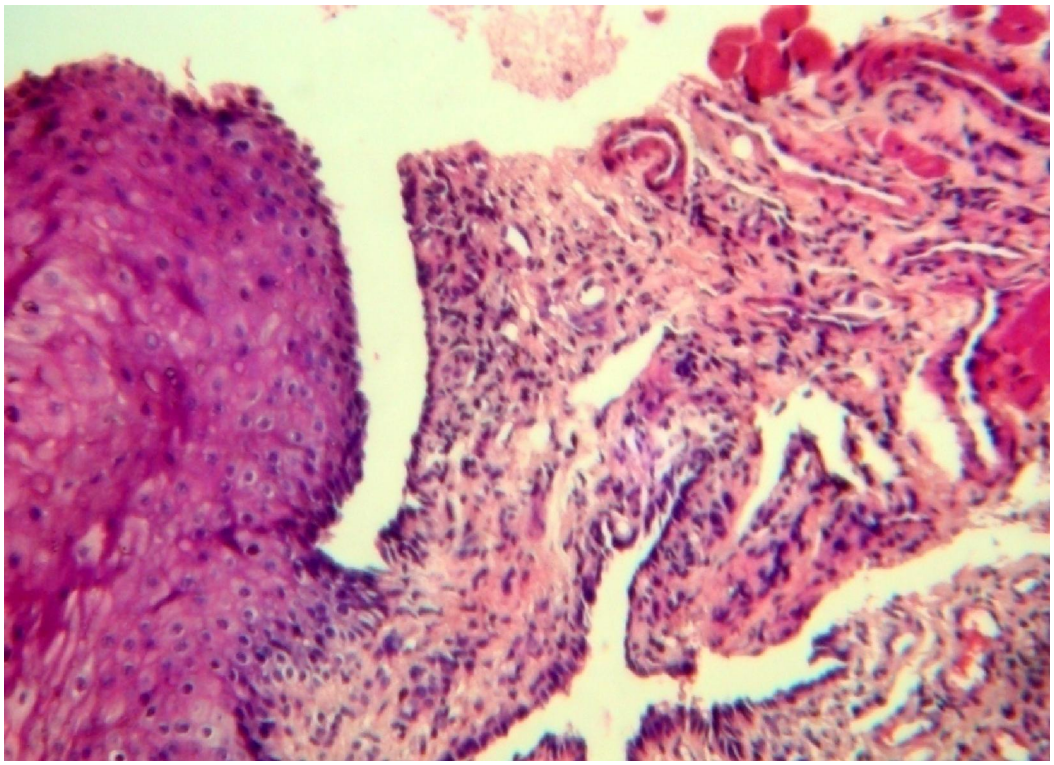
HIGH POWER VIEW (40X) – Acantholytic cells &
Intact basal cell layer



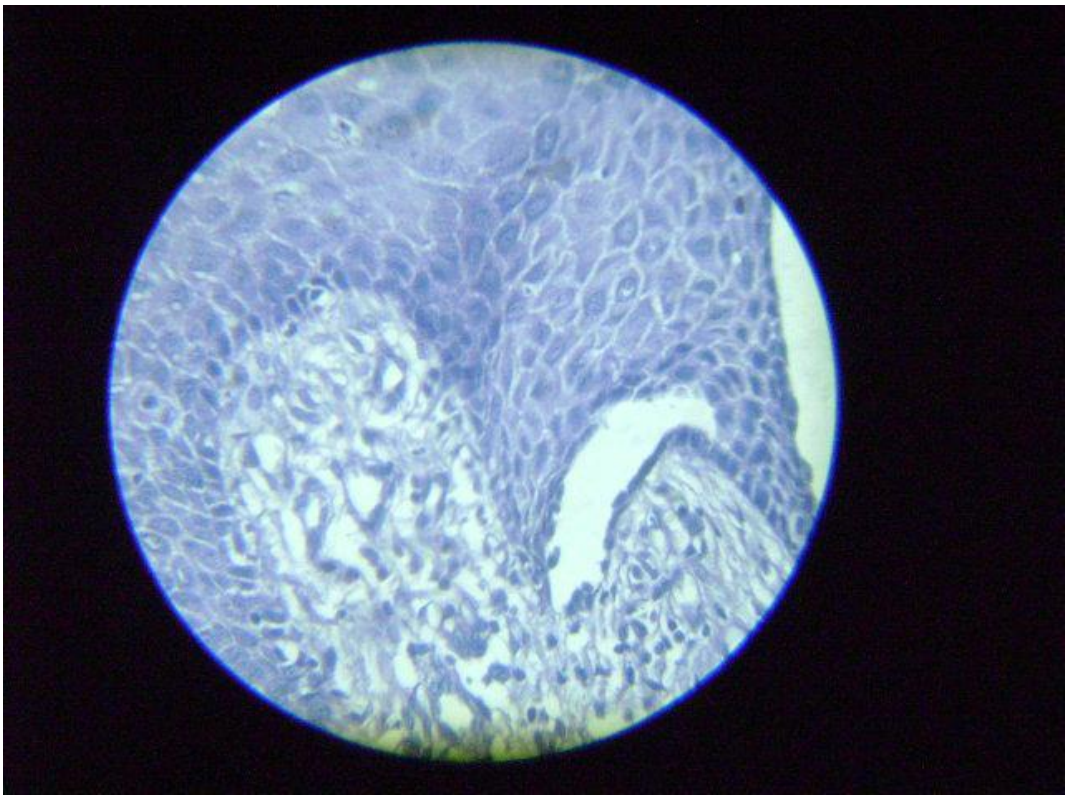
HPE- SUPRABASAL BULLA IN TONGUE (10x)



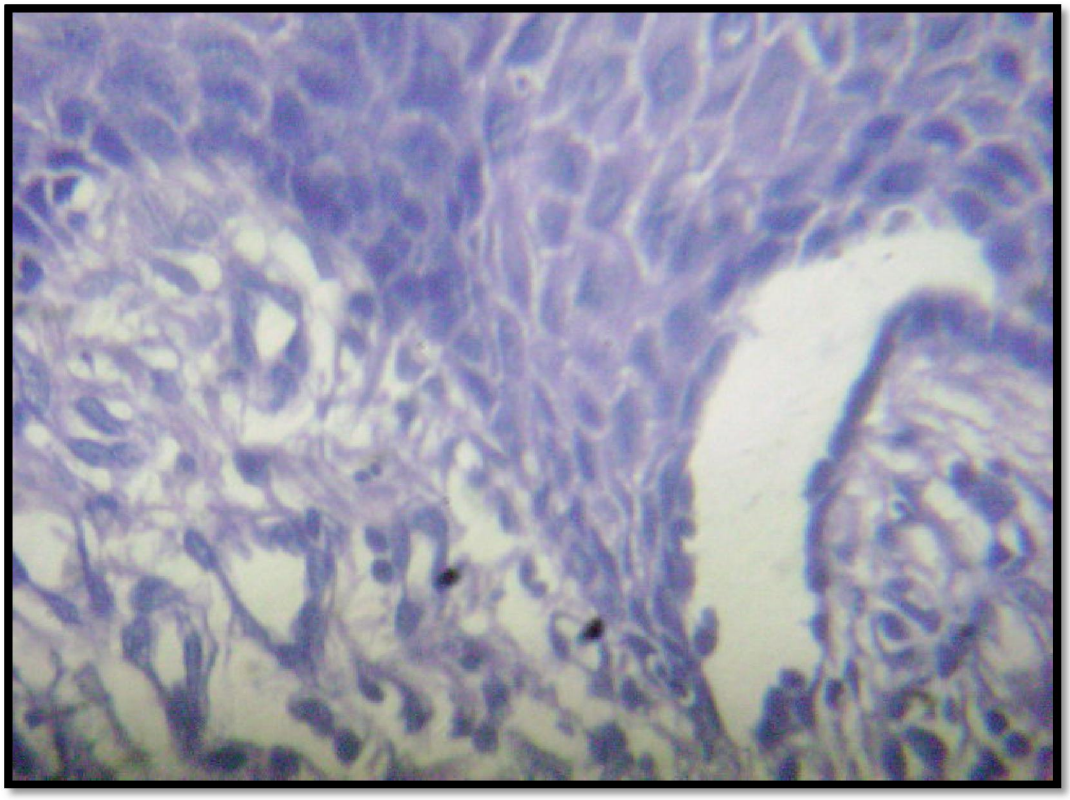
HPE- SUPRABASAL BULLA IN TONGUE (40x)



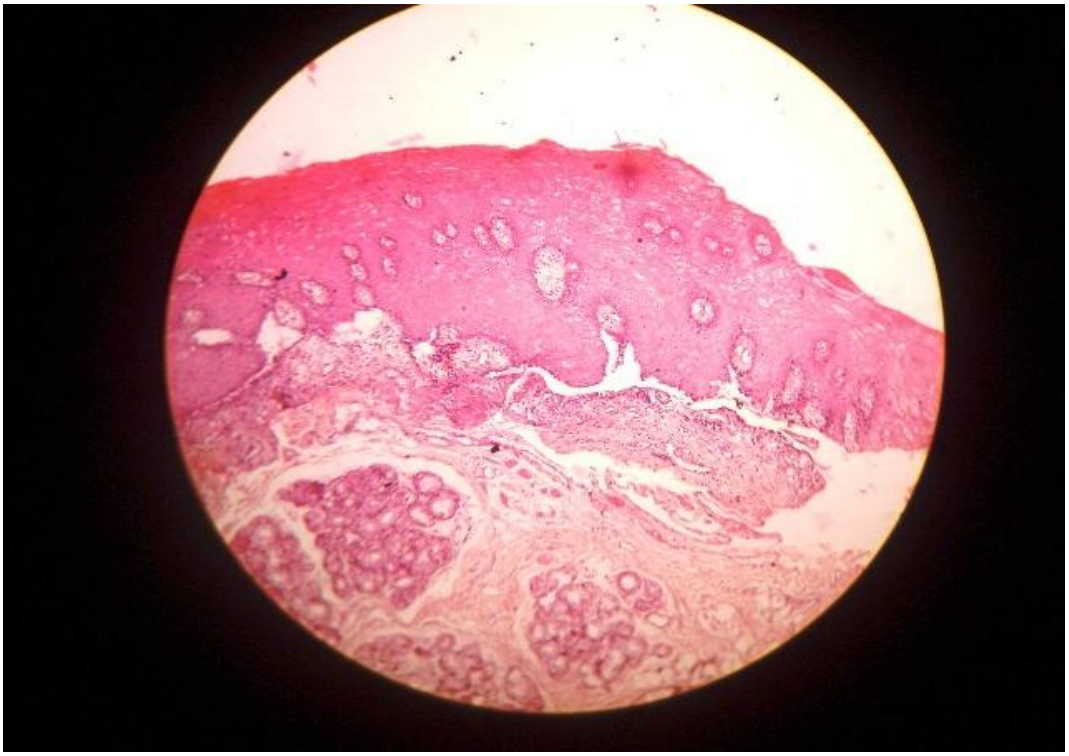
HPE-PEMPHIGUS VEGETANS WITH HYPERPLASTIC EPITHELIUM AND SUPRABASAL SEPARATION (10X)



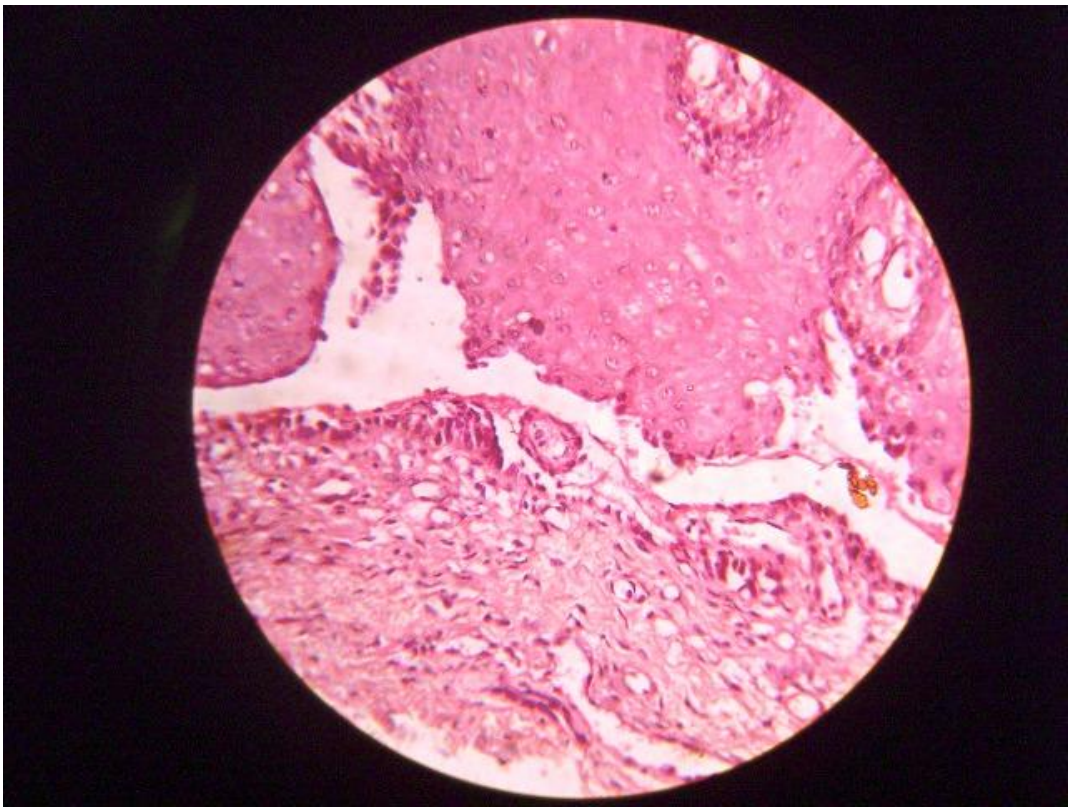
PEMPHIGUS VEGETANS (40X)



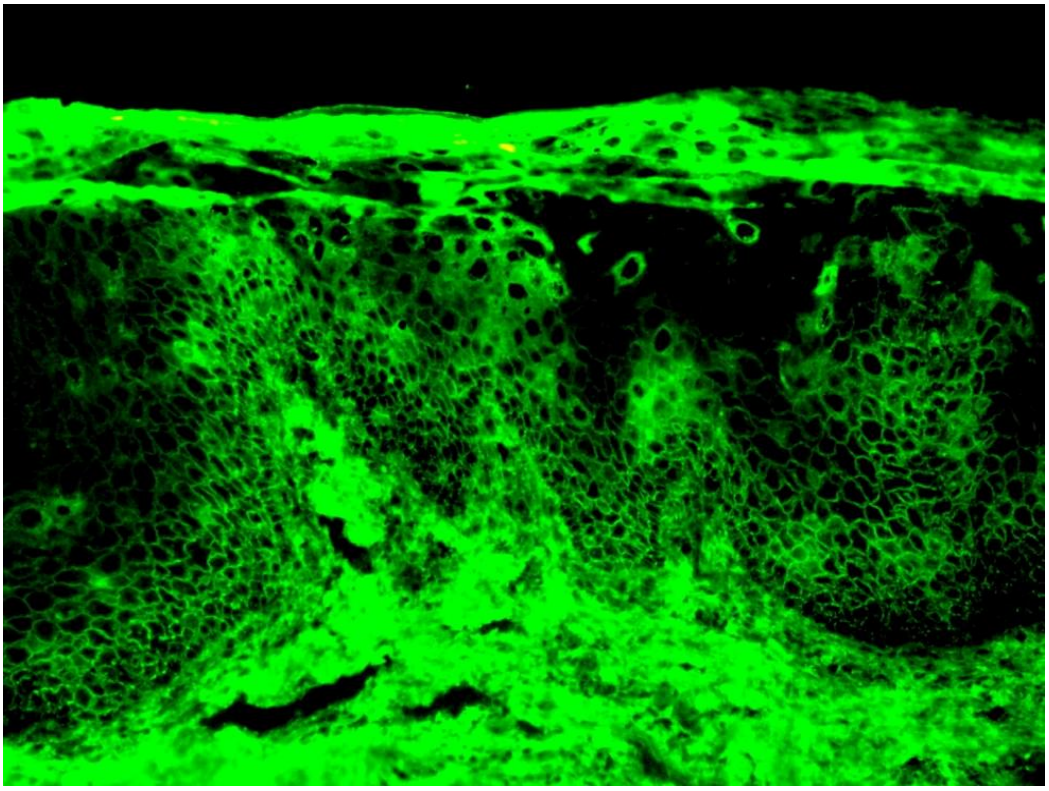
HPE- SUBEPITHELIAL SEPARATION IN BULLOUS PEMPHIGOID(10X)



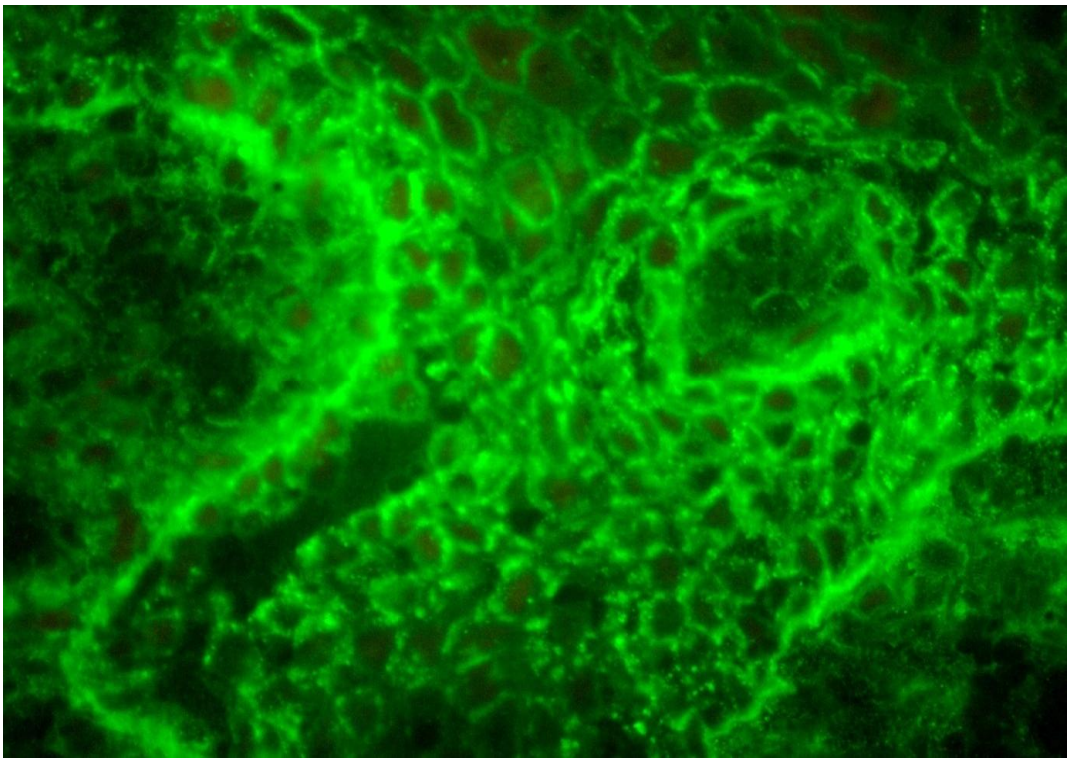
BULLOUS PEMPHIGOID (40X)



DIRECT IMMUNOFLUORESCENCE STUDY IN PEMPHIGUS VULGARIS- FISH NET PATTERN



DIRECT IMMUNOFLUORESCENCE STUDY IN PEMPHIGUS VEGETANS- FISH NET PATTERN



Clinical and histopathological (oral mucosal biopsy) correlation:

Out of the 53 skin biopsy proven patients of pemphigus vulgaris with both skin and oral involvement, typical suprabasal cleavage was seen in 50 patients in oral biopsy (94.3% correlation). Intraepidermal cleavage was seen in 2 patients and in the remaining 1 case, the biopsy had non-specific. In all these 3 patients, the mucosal biopsy specimen were subjected to direct immunofluorescence study and were confirmed as pemphigus.

In pemphigus vegetans and bullous pemphigoid, the correlation was 100% with respect to the level of cleavage. In both the two patients with Dermatitis herpetiformis, the oral mucosal biopsies did not correlate with the skin biopsy findings. The direct immunofluorescence of the mucosal biopsy specimen were also negative.

DRUG INDUCED VESICULOBULLOUS DERMATOSES:

Among the total 252 patients, 12 patients were drug induced vesiculobullous dermatoses. The various patterns, their age and sex distribution are tabulated (Table 12).

Table -12. Drug induced vesiculobullous dermatoses.

Age (years)	EM		SJS		TEN		Bullous FDE		Total
	With oral lesions	Without oral lesions	With oral lesions	Without oral lesions	With oral lesions	Without oral lesions	With oral lesions	Without oral lesions	
<20	1	0	2	0	0	0	0	0	3
21-30	2	0	0	0	2	0	0	0	4
31-40	0	0	0	0	2	0	0	1	3
41-50	0	0	0	0	0	0	0	0	0
51-60	1	0	1	0	0	0	0	0	2
Total	4	0	3	0	4	0	0	1	12

About 83.3% of the patients (10 of the 12 patients) were below forty years of age. The mean age for EM was 31.75 years, 29.75 years for Toxic epidermal necrolysis (Range: 23 – 32 years) and 31 years for Stevens Johnson syndrome (Range: 18 – 58 years).

Sex distribution:

Totally there were 7 male and 5 female patients. The male to female ratio was 1.4 : 1. The male to female ratio of EM was 1:3 and that of TEN was 1:3 whereas in SJS, it was 2:1.

Oral mucosal involvement (Table 14):

Lips were the most common sites involved (100%) followed by tongue (30%).

Table 14: Oral mucosal involvement

	Lips	Buccal mucosa	Tongue	Palate
EM	4	2	2	0
SJS	3	0	0	1
TEN	3	0	1	1
Total	10	2	3	2

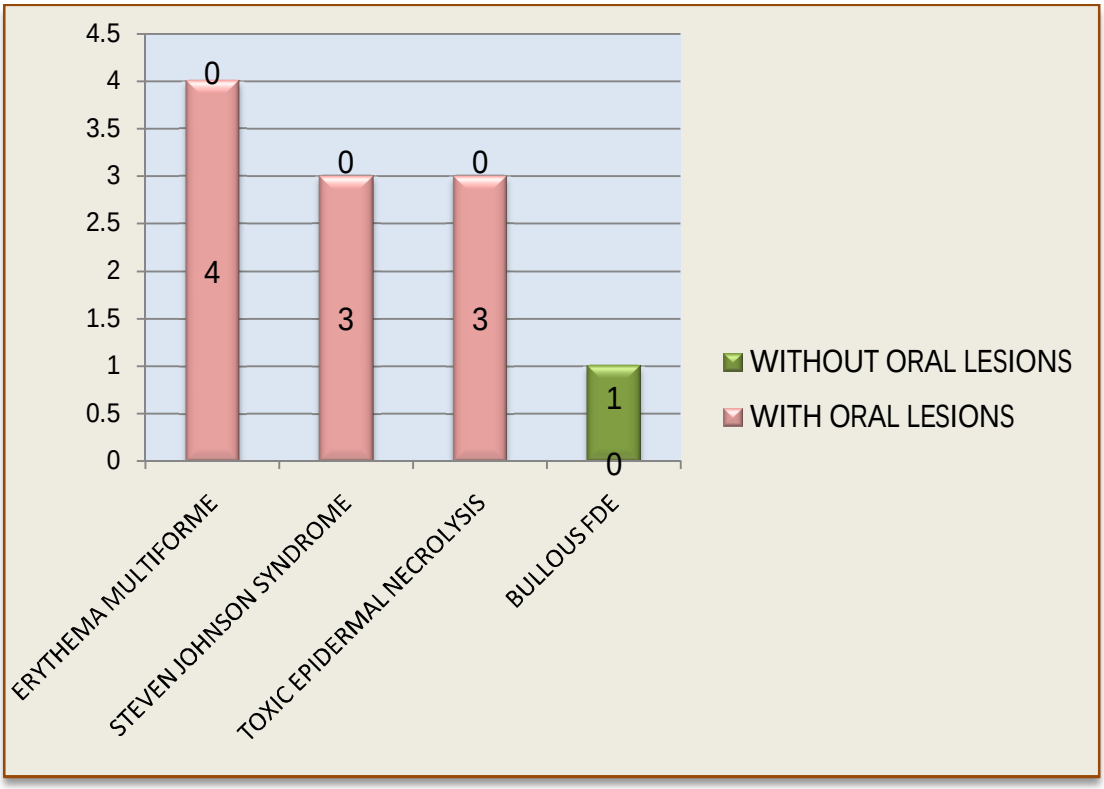
Onset of lesions in the skin & oral cavity:

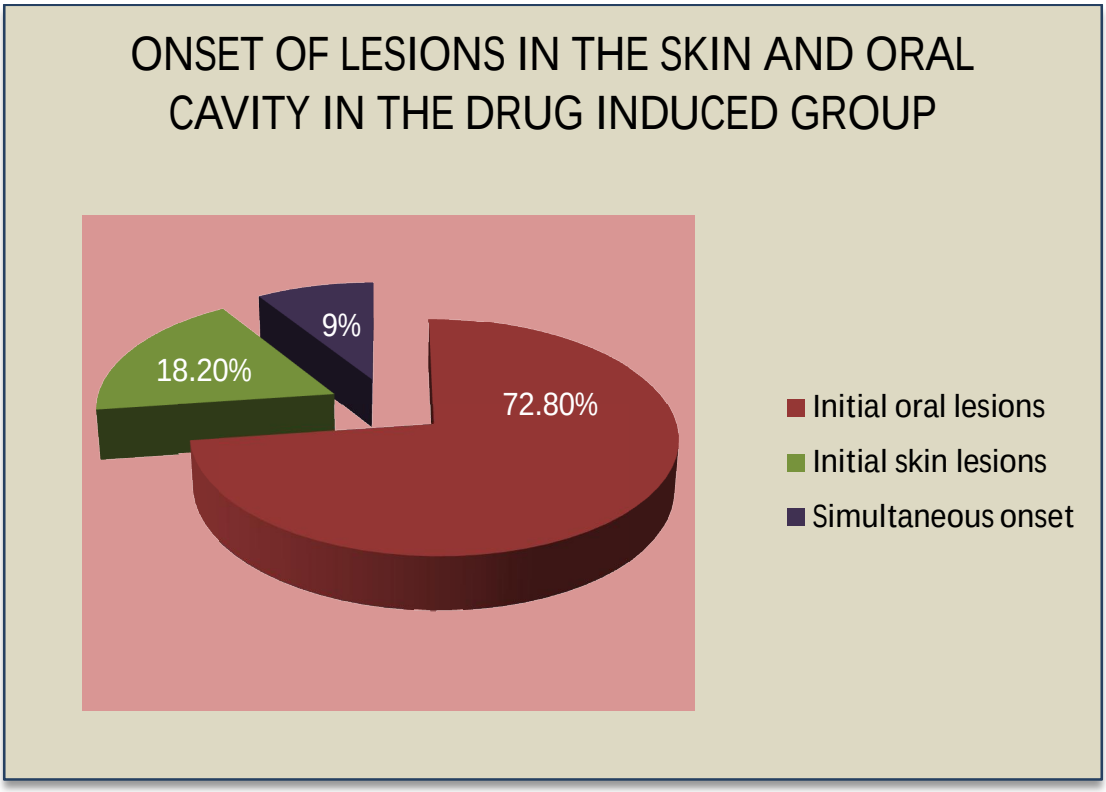
Among the 11 patients with both skin and oral mucosal involvement, oral lesions were the first to get involved in 8 patients (72.8%) followed by skin involvement in 2 patients (18.2%) and 1 patient had simultaneous involvement of both (9%). The average time interval between the onset of oral and skin lesions among those who had first involvement in the oral cavity was 2 days and for those who had skin involvement first, it was 1 day.

Offending agent (Table 13):

Dermatoses	Drugs
EM	Phenytoin, Amoxycillin, Cephalexin.
SJS	Cefotaxime, Diclofenac, Cotrimoxazole.
TEN	NSAIDS, Diclofenac, Carbamazepine (two patients).
FDE	Paracetamol.

DRUG INDUCED VESICULOBULLOUS CONDITIONS





ORAL ERYTHEMA MULTIFORME

ORAL ERYTHEMA MULTIFORME- SWELLING OF LIPS WITH HEMORRHAGIC CRUSTING

STEVENS-JOHNSON SYNDROME

TOXIC EPIDERMAL NECROLYSIS – ORAL AND CONJUNCTIVAL LESIONS

Discussion

DISCUSSION

Acquired vesiculobullous dermatoses constituted 0.29% of the total OPD patients. Among these, oral lesions were seen in 69.4% of the patients. In the study conducted by Nada M. Suliman et al[132] done in 544 patients in Sudan, oral lesions were seen in 72.2% of the patients which is comparable to our study.

Viral infections formed the major part of the vesiculobullous dermatoses, constituting about 50% followed by autoimmune dermatoses (45%). In the same study of Nada M. Suliman et al, viral infections and autoimmune dermatoses constituted 31.2% and 65.6% of the total vesiculobullous dermatoses respectively.[132] This variation can be explained by the difference in patients' willingness to seek medical care for a common ailment like recurrent herpes labialis which can alter the prevalence in hospital based studies.

VIRAL INFECTIONS:

Herpes simplex was the most common viral infection found among the patients of vesiculobullous dermatoses (77% of the total viral infections) followed by varicella zoster virus (19.9%) infection while Nada M. Suliman et al have reported varicellosis being more common in their study.[132]

Age:

Majority of the viral infections were seen before the 4th decade of life (61.9%). Herpes simplex was seen in all age groups with peak values in the 3rd and 4th decade. Mean age was 34.9 years in males and 29.02 years in females. About 70% of herpes simplex patients were seen in <40 years of age in consistence with the Hashido et al study.[133]

Twenty out of the 21 patients with herpes zoster (95.2%) were above 40 years of age (Mean – 53.85 years). Gonzaga et al have reported a similar occurrence of majority of the patients being above 40 years of age.[134] The mean age for herpes zoster reported by Oh et al was 50.35 years.[135] Hand, foot & mouth disease was exclusively seen in the first decade ranging from 2 – 10 years (Mean – 8 years) whereas Sarma et al have reported exclusive occurrence of the disease in 1 to 12 years age group[136] and C. H. Tay et al have reported >90% occurrence of the disease among children in the first decade.[137]

Sex:

There was no gender predominance as a whole or in any of the individual viral infections. Heininger et al have reported similar observation in varicella[138] while Shetty et al have documented a male to female ratio of 7:1 which has been attributed by them to an outbreak in a

boy's school during their study period.[139] While Sarma et al have reported a slight predilection for males in their study on hand, foot and mouth (M:F- 1.2:1), [136] C. H. Tay et al have reported an equal distribution.[137]

Oral lesions:

In Herpes simplex, lips were the predominant sites to be involved, seen in 85 patients (97.7%). Tongue was involved in all the primary and recurrent intraoral herpes patients (5.7%). Gingiva was the least to get involved (1.1%).

None of the 4 patients of Varicella had enanthem. Kolokotronis et al have reported 74% of a total 62 patients with mucosal lesions.[140] As our study had only a small group, comparison cannot be done. Out of the 21 herpes zoster patients, oral lesions were found in 3 of them (14.3%). Maxillary branch was involved in one patient (4.8%) with vesicles over left half of the palate and upper labial mucosa. In the study done by Latheef et al, maxillary branch involvement was seen in 7.3% of the total 205 herpes zoster patients,[141] compared to only 1 out of 21 (4.8%) patients in this study. Ramsay Hunt syndrome with lower motor neuron facial palsy and vesicles in the ipsilateral pinna & tongue was found in

two patients (9%) whereas in the study conducted by Thappa et al in 107 patients, only one case was reported (0.9%).[142]

Of the 4 patients of Hand, foot & mouth disease seen, two patients had oral lesions (50%). Tongue was involved in one patient and lips in the other. This differs from the Sarma et al study in which 86.8% of the total 38 patients, had oral lesions.[136]

AUTOIMMUNE BULLOUS DISORDERS:

PEMPHIGUS VULGARIS:

Age:

About 52.9% of the patients were in the 4th (27.9%) and 5th decade (25%) in our study (average – 43.45 years). In the study conducted by Thorakkal Shamim et al in Calicut, the mean age was 42.73 years[143] while in the Esmaili N et al study, the mean age at the time of presentation was 41.5 years[144] which were all almost similar to this study.

Sex distribution:

Females were most affected in our study (M : F – 1 : 3.9). The difference is slightly higher when compared to the studies done by Alonso et al (male to female ratio of 1 : 2.5),[28] Langan et al (male to female ratio was1:2),[145] Esmaili N et al (male to female ratio of

1 : 1.59)[144] and Deval Vora et al (male to female ratio of 1 : 1.48 in South India).[146]

Mucosal involvement:

Oral cavity was the most affected mucosa (89.7% of pemphigus vulgaris patients) followed by genital (20.6%), nasal mucosa (11.8%) and conjunctiva (2.9%) in concurrence with the Deval Vora et al study.[146]

Oral cavity involvement:

Oral lesions were seen in 61 out of the 68 patients of pemphigus vulgaris (89.7%) of which 53 patients (78%) had both skin and oral lesions, 7 (10.3%) had only skin lesions and 8 (11.7%) had only oral lesions whereas in the Esmaili N et al study, 67.9% of patients had both skin and oral involvement, 6.4% of patients had only skin lesions and oral involvement was exclusively seen in 25.7% of the patients.[144] Abdolsamadi et al have reported isolated oral involvement in 47% of their patients.[147] These studies were conducted in dental OPDs, to which patients tend to attend when there are no skin lesions and hence have reported a higher prevalence.

Morphology of oral lesions:

Erosions were predominantly seen in 93.4% of our patients, while rest of them showed both erosions as well as few vesicles, similar to the observation made by Alonso et al who have reported that 92.8% of their patients had erosions.[28]

Site of involvement in the oral cavity:

Buccal mucosa was the commonest site to get affected (44.3%) followed by lips, palate and tongue similar to the study conducted by Thorakkal Shamim et al [143] whereas in the study conducted by Robinson et al, majority of oral lesions were in the gingival.[148] In the Laskaris et al study, majority of lesions were in the palate.[149]

Extent of oral lesions:

About 35 patients (57.4%) had Grade III involvement of the oral cavity followed by Grade II (19 patients, 31.1%) and Grade 1 (7 patients, 11.5%) similar to the observation made by Thorakkal Shamim et al [143] and the Alonso et al in their studies.[28]

Onset of the lesions in skin and oral cavity:

The most common initial localization of the disease was the oral cavity, seen in 41 patients (60.3%), followed by skin in 17 patients (25%)

and simultaneous onset of both in 10 patients (14.7%). This observation is similar to the study done by Ameneh Yazdanfar et al[150] where oral lesions were the first to get involved in 60% patients and approximately coincides with the Thorakkal Shamim et al study in which the corresponding values are 53.52%, 23.94% and 22.53% respectively.[143] In the study done by Ali et al in the central Iran, oral mucous membrane involvement was the first to get involved in 74% of the patients.[151]

Candidal superinfection:

About 86.9% of patients with oral lesions had secondary oral candidiasis confirmed by the presence of pseudohyphae and spores in the 10% KOH mount. In the Chmurova et al study, only 45.2% (14 out of 31) were found to have candidal superinfection.[152] This higher incidence is due to poor oral hygiene, as the painful nature of the lesions hinders in maintaining good hygiene and secondary to the use of steroids and antibiotics for treatment. This has to be taken care of during the management of oral pemphigus.

Clinical and histopathological correlation:

Out of the 53 skin biopsy proven patients of pemphigus vulgaris with both skin and oral involvement, typical suprabasal cleavage, acantholytic cells were seen in 50 patients in oral biopsy (94.3%

correlation with skin biopsy). Intraepithelial blisters with acantholytic cells were seen in 52 patients (98%) compared to 100% in the study conducted by Alonso et al.[28]

Bullous pemphigoid:

Age:

Majority of the bullous pemphigoid patients were seen in 6th and 7th decades. This coincides with the study conducted by Budimir et al in which most of the patients were between 70 – 90 years age group.[153]

Sex:

There was no sexual predilection was seen in this study which is in similar to the study done by Budimir et al.[153]

Oral cavity involvement:

Oral cavity involvement was seen in 6 out of the 22 (27%) patients and is slightly higher than the study conducted by Budimir et (17%)[153] and Chang et al (12.8%).[154] In the study done by Arambašin et al, oral mucosal involvement was seen in 40% which supports our study.[69]

Site of involvement in the oral cavity:

Buccal mucosa (83.3%) followed by gingiva (50%) were the commonest sites to be involved similar to the observation made by Budimir et al in their study.[153]

Onset of the lesions in skin and oral cavity:

Two patients had their first involvement of the disease in the oral cavity (9%) compared to 5% in the Budimir et al study.[153] None of the patients had isolated mucosal involvement in both studies.

DRUG INDUCED VESICULOBULLOUS DERMATOSES:

Among the total 12 patients, 4 had erythema multiforme, 3 had Stevens Johnson syndrome, 4 had Toxic epidermal necrolysis and 1 had bullous FDE. All the patients had history of drug intake prior to the onset of lesions. One patient was on Etoposide and Ifosfamide which has not been reported in the literature to cause EM.

Age:

Out of the 12 patients, 10 patients (83.3%) were below forty years of age. The mean age for EM was 31.75 years which concurs with the study done by Goncalves et al in which majority of EM patients in 20-40 years age group.[155] The mean age for Toxic epidermal necrolysis was

29.75 years (Range: 23 – 32 years) and 31 years for Stevens Johnson syndrome (Range: 18 – 58 years) similar to the Sanmarkan et al study, in which maximum number of SJS/TEN patients were in the age group of 11-30 years.[156] Schöpf et al reported a mean age of 25 years in TEN which is similar to our study.[157]

Sex:

The male to female ratio of the total patients was 1.4:1. The male to female ratio of EM was 1:3. In the Goncalves et al study, females were the most affected (62%).[155] The male to female ratio was 1:3 for TEN and 2:1 for SJS. In the Schöpf et al study, the corresponding values are 1:2 and 2:1 which are almost similar.[157] Similar findings were observed in the Sanmarkan et al study.[156]

Oral mucosal involvement:

The oral cavity was involved in 11 out of the 12 patients (91.7%). Lips were the most frequently involved sites, seen in 100% of the patients with oral lesions, followed by the tongue (30%). Among the patients with EM in this study, oral lesions were seen in all patients while Goncalves et al reported only 33% of patients with oral involvement.[155]

Offending drugs:

NSAIDs were the most common drugs precipitating the disease in 4 out of the total 12 patients (33.3%). The drugs most commonly involved were antibiotics in SJS (67%) followed by analgesics (33%). For TEN, analgesics and antiepileptics were the offending agents, constituting 50% each which concurred with the study conducted by Schöpf et al.[157]

Conclusion

CONCLUSION

1. Acquired vesiculobullous dermatoses constituted 0.29% of the total patients attending Dermatology OP division and 69.4% of them had oral involvement.

2. Viral infections are the most common subdivision of vesiculobullous dermatoses. Majority of the viral infections were seen before the 4^{th} decade of life. No sex predilection was seen as a whole or in any of the individual viral infections. Lips were the most common sites to get involved in viral infections.

3. Herpes simplex was the most common viral infection found mainly in <40 years of age while herpes zoster was seen above 40 years of age.

4. Autoimmune bullous disorders constituted 45.2% of the total patients and 63.2% of these patients had oral lesions. The age distribution varied from 17–85 years. The male to female was 1: 2.4.

5. Pemphigus vulgaris was the most common autoimmune bullous dermatoses followed by bullous pemphigoid. Pemphigus vulgaris was most commonly seen in 4^{th} decade followed by 5^{th} decade while bullous pemphigoid was more common in the seventh followed by sixth decade. Oral mucosal involvement was seen in 89.7% of pemphigus vulgaris and 27% of bullous pemphigoid patients.

6. The male to female ratio was 1 : 3.9 in pemphigus vulgaris and 1 : 1.4 in bullous pemphigoid.

7. Buccal mucosa was the most common site to get involved in both pemphigus vulgaris and bullous pemphigoid. Isolated oral mucosal involvement was found in 11.8% of patients with pemphigus vulgaris. The oral lesions preceded the onset of skin lesions in 62.3% of patients and the average time interval between the onset of each was 36.6 days.

8. Early diagnosis can be made by biopsy of the oral lesions in autoimmune vesiculobullous dermatoses in those patients with first involvement in the oral mucosa.

9. Drug induced vesiculobullous dermatoses constituted 4.8% of the total patients. Antimicrobials and analgesics were the most common offending agents. Majority of the patients were below forty years of age. The male to female ratio was 1.4:1.

10. The oral cavity was involved in 91.7% of the patients. Lips were the most frequently involved sites seen in 100% of the patients with oral lesions.

11. Early diagnosis and prompt treatment will help reducing the morbidity and mortality in drug induced dermatoses.

Annexures

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Master Charts

Viral Infections

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
z	34	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
2	9	M	HS	1 day	P	P	A	A	P	A	A	P	A	Nil	Nil	MNG	HSV 1
3	35	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
4	42	M	HS	2 day	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
5	28	M	HS	2 days	R	A	P	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
6	24	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
7	33	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
8	22	M	HS	5 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
9	32	F	HS	2 days	R	P	P	A	A	A	A	A	A	Nil	Nil	MNG	HSV 1
10	29	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
11	30	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
12	43	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
13	21	F	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
14	17	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
15	22	F	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
16	14	M	HS	7 days	P	P	A	A	P	P	A	A	A	Nil	Meningitis	MNG	HSV 1
17	27	M	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
18	21	F	HS	5 days	RIOH	P	A	P	P	A	A	A	A	Nil	Nil	MNG	HSV 1

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
19	18	F	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
20	42	M	HS	5 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
21	8	M	HS	2 days	P	P	A	P	P	P	A	A	A	Nil	Nil	MNG	HSV 1
22	27	M	HS	4 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	HSV 1
23	26	F	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
24	29	M	HS	2 days	R	A	P	P	A	A	A	A	A	Nil	Nil	Neg	HSV 1
25	32	F	HS	2 days	RIOH	P	A	P	P	A	A	A	A	Nil	Nil	MNG	HSV 1
26	52	M	HS	1 day	R	A	A	A	A	A	A	A	A	Nasal	Nil	Neg	HSV 1
27	57	M	HS	2 days	R	A	A	A	A	A	A	A	A	Nasal	Nil	MNG	HSV 1
28	46	M	HS	2 days	R	A	A	A	A	A	A	A	A	Nasal	Nil	MNG	HSV 1
29	28	M	HS	3 days	R	A	A	A	A	A	A	A	A	Genital	Nil	Neg	Not done
30	19	M	HS	3 days	R	A	P	P	A	A	A	A	A	Nil	Nil	MNG	Not done
31	31	F	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
32	14	M	HS	4 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
33	31	F	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
34	35	F	HS	2 days	R	P	P	A	A	A	A	A	A	Nasal	Nil	Neg	Not done
35	35	F	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
36	24	F	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
37	38	M	HS	3 days	R	P	P	A	A	A	A	A	A	Nasal	Nil	Neg	Not done
38	18	F	HS	4 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
39	30	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
40	21	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
41	25	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
42	31	M	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
43	20	M	HS	6 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
44	18	F	HS	2 days	R	A	P	P	A	A	A	A	A	Nasal	Nil	Neg	Not done
45	45	F	HS	5 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
46	29	M	HS	3 days	R	P	P	P	A	A	A	A	A	Nil	Nil	MNG	Not done
47	47	M	HS	4 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
48	52	F	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
49	45	F	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
50	42	M	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
51	13	F	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
52	31	M	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
53	24	F	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
54	13	M	HS	6 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
55	19	M	HS	2 days	P	P	A	P	A	A	A	A	A	Genital	Nil	MNG	Not done
56	12	F	HS	4 days	R	A	P	P	A	A	A	A	A	Nil	Nil	Neg	Not done
57	32	F	HS	5 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
58	32	F	HS	5 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
59	33	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
60	25	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
61	54	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
62	34	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
63	17	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
64	55	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
65	50	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
66	21	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
67	44	F	HS	2 day	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
68	73	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
69	42	M	HS	3 days	P	A	A	A	A	A	A	A	A	Genital	Nil	MNG	Not done
70	32	M	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
71	40	F	HS	5 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
72	43	M	HS	2 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
73	68	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
74	34	M	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
75	11	F	HS	5 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
76	36	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
77	62	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
78	56	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
79	67	F	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
80	36	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
81	23	M	HS	2 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
82	65	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
83	37	F	HS	3 days	R	P	P	A	A	A	A	A	A	Nasal	Nil	MNG	Not done
84	45	M	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
85	24	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
86	20	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
87	22	F	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
88	17	M	HS	3 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
89	43	M	HS	1 day	R	A	A	P	A	A	A	A	A	Nasal	Nil	MNG	Not done
90	52	M	HS	5 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
91	34	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
92	39	F	HS	5 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
93	72	F	HS	4 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
94	34	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
95	62	M	HS	4 days	R	A	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
96	43	F	HS	5 days	R	P	A	P	A	A	A	A	A	Nil	Nil	Neg	Not done
97	18	M	HS	3 days	R	A	A	P	A	A	A	A	A	Nil	Nil	MNG	Not done
98	28	M	CP	2 days	P	P	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
99	60	M	CP	4 days	P	P	P	A	A	A	A	A	A	Nil	Meningo encephalitis	Neg	Not done
100	18	F	CP	2 days	P	P	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
101	12	M	CP	1 day	P	P	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
102	32	F	HZ	3 days	P	P	P	P	A	P	A	A	A	Nil	Nil	MNG	Not done
103	58	M	HZ	4 days	P	A	P	P	P	A	P	A	A	Nil	Lt facial nerve palsy	MNG	Not done
104	7	M	HZ	3 days	P	P	P	P	P	A	P	A	A	Nil	Lt facial nerve palsy	Neg	Not done
105	42	F	HZ	4 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
106	53	M	HZ	2 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
107	65	F	HZ	2 days	P	P	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done

S No.	AGE	SEX	DIAGNOSIS	DURATION	PRIMARY/ RECURRENT	CONSTITUTIONAL SYMPTOMS	SKIN	ORAL CAVITY						OTHER MUCOSAE	SYSTEMIC INVOLVEMENT	Tzanck	CELL CULTURE
								LIPS	TONGUE	PALATE	FLOOR OF THE MOUTH	GINGIVA	BUCCAL MUCOSA				
108	39	M	HZ	1 day	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
109	68	M	HZ	2 days	R	A	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
110	54	M	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
111	63	F	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
112	64	F	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
113	48	F	HZ	3 days	P	P	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
114	52	F	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
115	57	F	HZ	2 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
116	72	M	HZ	4 days	P	A	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
117	47	M	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
118	69	F	HZ	5 days	R	A	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
119	51	M	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	MNG	Not done
120	69	M	HZ	4 days	P	P	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
121	72	M	HZ	4 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
122	49	F	HZ	3 days	P	A	P	A	A	A	A	A	A	Nil	Nil	Neg	Not done
123	10	F	HF	3 days	_	P	P	P	A	A	A	A	A	Nil	Nil	_	Not done
124	2	F	HF	1 day	_	P	P	A	P	A	A	A	A	Nil	Nil	_	Not done
125	8	M	HF	3 days	_	P	P	A	A	A	A	A	A	Nil	Nil	_	Not done
126	8	M	HF	2 days	_	P	P	A	A	A	A	A	A	Nil	Nil	_	Not done

Autoimmune Bullous Disorders

S. No.	DIAGNOSIS	AGE	SEX	DURATION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
1	PVu	35	F	4 yr	P	E	P	A	P	P	A	A	A	3	Positive	Oral	Tongue	1 mo	Gen	SupB	SupB	P	
2	PVu	46	M	1 yr	P	E	A	A	P	P	A	A	A	2	Positive	Oral	Tongue	1 mo	Nil	SupB	SupB	P	
3	PVu	20	F	1 yr	P	E	P	A	P	P	P	A	A	4	Positive	Both	Buc mucosa	_	Nas, Conj, Gen	SupB	SupB	P	
4	PVu	28	F	2 yr	P	E	P	A	A	P	A	A	P	3	Positive	Oral	Pharynx	3 mo	Nil	SupB	SupB	P	
5	PVu	30	F	2 yr	P	E	A	A	P	P	A	A	A	2	Positive	Skin	Buc mucosa	1 yr	Nil	SupB	IeB	P	ICF+
6	PVu	41	F	10 mo	P	E	A	P	A	P	P	A	A	3	Negative	Oral	Buc mucosa	2 mo	Nas, Gen	SupB	SupB	P	
7	PVu	27	F	1 yr	P	V	A	A	A	P	A	A	P	2	Positive	Both	Buc mucosa	_	Nil	SupB	SupB	P	
8	PVu	75	F	2 yr	P	E	P	A	A	P	P	A	A	3	Positive	Oral	Lips	10 days	Nil	SupB	SupB	P	
9	PVu	29	F	3 mo	P	E	P	P	P	P	P	A	A	5	Negative	Oral	Buc mucosa	1 wk	Nas, Conj, Gen	SupB	SupB	P	
10	PVu	55	F	4 yr	P	E	P	A	A	A	P	A	A	2	Positive	Oral	Lips	1 mo	Nil	SupB	Non specific	P	ICF+
11	PVu	56	F	3 yr	P	E	P	A	A	P	P	A	A	3	Positive	Oral	Palate	6 mo	Nil	SupB	SupB	P	
12	PVu	68	F	7 yr	P	E	P	A	A	P	A	P	A	3	Positive	Oral	Buc mucosa	1 mo	Nil	SupB	SupB	P	
13	PVu	62	F	3 yr	P	E	P	A	A	A	A	A	A	1	Positive	Oral	Lips	3 mo	Nil	SupB	SupB	P	
14	PVu	32	F	3 yr	P	E	P	A	A	P	A	P	A	3	Positive	Skin	Lips	1 yr	Nil	SupB	SupB	P	

S. No.	DIAGNOSIS	AGE	SEX	DURATION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
15	PVu	54	M	1½ yr	P	E	P	A	P	P	P	A	A	4	Positive	Both	Lips	_	Nil	SupB	SupB	P	
16	PVu	50	F	10 yr	P	E	P	A	A	P	A	A	A	2	Positive	Skin	Buc mucosa	10 days	Nil	SupB	SupB	P	
17	PVu	28	F	1½ yr	P	E	P	P	A	P	P	A	A	4	Positive	Oral	Lips	6 mo	Nil	SupB	SupB	P	
18	PVu	40	F	3 yr	P	E	P	A	A	A	P	P	P	4	Positive	Oral	Lips	1 mo	Nil	SupB	SupB	P	
19	PVu	35	F	8 mo	P	E	P	A	P	P	P	P	A	5	Negative	Oral	Tongue	1 mo	Nil	SupB	SupB	P	
20	PVu	43	M	1½ mo	P	E	A	A	A	P	P	A	A	2	Positive	Both	Buc mucosa	_	Nil	SupB	SupB	P	
21	PVu	45	M	6 mo	P	E	P	A	A	P	P	A	A	3	Positive	Oral	Buc mucosa	2 mo	Nil	SupB	SupB	P	
22	PVu	40	F	2 mo	P	V	P	A	A	P	P	P	A	4	Negative	Both	Buc mucosa	_	Nil	SupB	SupB	P	
23	PVu	30	F	3 mo	P	E	P	P	A	P	A	A	A	3	Negative	Both	Buc mucosa	_	Nil	SupB	SupB	P	
24	PVu	62	M	2½ yr	P	E	P	A	A	P	P	A	A	3	Positive	Oral	Buc mucosa	10 days	Nil	SupB	SupB	P	
25	PVu	60	F	6 yr	P	E	P	P	P	P	A	A	A	4	Positive	Both	Tongue	_	Nil	SupB	SupB	P	
26	PVu	37	F	3 yr	P	E	P	A	P	P	A	A	A	3	Positive	Oral	Tongue	10 days	Nil	SupB	SupB	P	
27	PVu	55	F	6½ mo	P	E	P	A	P	P	A	A	A	3	Positive	Oral	Buc mucosa	10 days	Nil	SupB	IeB	P	ICF+
28	PVu	55	F	10 mo	P	E	P	A	P	P	P	A	A	4	Positive	Oral	Tongue	1 wk	Nil	SupB	SupB	P	
29	PVu	32	M	1½ yr	P	E	P	A	A	A	A	A	P	2	Positive	Skin	Lips	6 mo	Nas, Gen	SupB	SupB	P	ICF+
30	PVu	50	F	11 mo	P	E	P	P	P	P	A	A	A	4	Positive	Oral	Buc mucosa	1 mo	Nil	SupB	SupB	P	

S. No.	DIAGNOSIS	AGE	SEX	DURA TION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
31	PVu	40	F	3 yr	P	E	A	A	P	P	P	A	A	3	Positive	Both	Tongue	_	Gen	SupB	SupB	P	
32	PVu	62	F	1 yr	P	E	P	A	A	P	A	P	A	3	Positive	Oral	Buc mucosa	1 wk	Nil	SupB	SupB	P	
33	PVu	27	M	2 yr	P	E	P	A	P	P	P	A	A	4	Positive	Oral	Tongue	2 mo	Nas	SupB	SupB	P	
34	PVu	42	M	1 yr	P	V	A	A	P	P	A	A	A	2	Positive	Skin	Buc mucosa	1½ mo	Gen	SupB	SupB	P	
35	PVu	43	F	10 yr	P	E	P	A	A	P	P	A	A	3	Positive	Oral	Buc mucosa	1 mo	Nas, Gen	SupB	SupB	P	
36	PVu	42	M	6 mo	P	E	P	A	A	P	P	A	P	3	Positive	Oral	Buc mucosa	1 wk	Nil	SupB	SupB	P	
37	PVu	60	F	4 yr	P	E	P	A	A	A	P	A	A	2	Positive	Oral	Lips	20 days	Gen	SupB	SupB	P	
38	PVu	35	F	6 mo	P	E	P	A	P	P	P	A	A	4	Positive	Skin	Buc mucosa	10 days	Nil	SupB	SupB	P	
39	PVu	35	F	2 yr	P	E	P	A	A	P	A	A	A	2	Positive	Oral	Lips	1 wk	Nas, Gen	SupB	SupB	P	
40	PVu	21	F	8 mo	P	E	A	A	A	P	P	P	P	4	Positive	Skin	Buc mucosa	2 mo	Nas, Gen	SupB	SupB	P	ICF+
41	PVu	50	F	1 yr	P	E	P	A	A	P	A	A	P	3	Positive	Both	Pharynx	_	Gen	SupB	SupB	P	
42	PVu	54	F	1½ yr	P	E	P	A	P	P	A	A	P	4	Positive	Skin	Buc mucosa	1 yr	Nil	SupB	SupB	P	
43	PVu	31	F	6 yr	P	E	P	A	A	P	A	A	A	2	Positive	Oral	Lips	1 wk	Nil	SupB	SupB	P	
44	PVu	50	F	8 yr	P	E	P	A	A	P	A	A	A	2	Positive	Both	Lips	_	Nil	SupB	SupB	P	
45	PVu	35	F	9 mo	P	E	A	A	A	P	A	A	A	1	Positive	Skin	Buc mucosa	1 mo	Nil	SupB	SupB	P	
46	PVu	28	M	2 mo	P	E	A	A	P	A	A	P	P	3	Negative	Skin	Buc mucosa	1 mo	Nil	SupB	SupB	P	ICF+

S. No.	DIAGNOSIS	AGE	SEX	DURATION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
47	PVu	55	F	6 mo	P	E	P	A	A	A	P	A	A	2	Positive	Oral	Buc mucosa	1 mo	Nil	SupB	SupB	P	
48	PVu	34	F	7 yr	P	E	P	A	A	A	A	A	A	1	Positive	Oral	Buc mucosa	2 wk	Gen	SupB	SupB	P	
49	PVu	50	F	2 wk	P	E	P	A	A	A	A	A	A	1	Negative	Oral	Lips	1 wk	Nil	SupB	SupB	P	
50	PVu	42	M	3½ yr	P	E	A	A	A	P	A	A	A	1	Positive	Oral	Tongue	2 wk	Nil	SupB	SupB	P	
51	PVu	24	M	2 yr	P	E	P	A	P	A	P	A	A	2	Positive	Oral	Lips	1 mo	Gen	SupB	SupB	P	
52	PVu	58	F	9 mo	P	E	A	A	A	P	P	A	A	2	Positive	Oral	Lips	1 mo	Nil	SupB	SupB	P	
53	PVu	35	F	5 yr	P	E	A	A	A	P	A	A	A	1	Positive	Oral	Lips	3 wk	Nil	SupB	SupB	P	
54	PVu	70	F	8 mo	A	E	P	A	P	P	P	A	A	4	Positive	_	Palate	_	Nil	_	SupB	P	ICF+
55	PVu	60	F	1 yr	A	E	P	A	A	P	A	A	A	2	Positive	_	Lips	_	Nil	_	SupB	P	ICF+
56	PVu	44	F	1 yr	A	E	P	A	A	A	A	A	A	1	Positive	_	Lips	_	Nil	_	SupB	P	ICF+
57	PVu	33	F	4 mo	A	E	P	A	P	A	A	A	A	2	Negative	_	Tongue	_	Nil	_	SupB	P	ICF+
58	PVu	45	F	3 yr	A	E	P	A	A	P	A	A	A	2	Positive	_	Lips	_	Nil	_	SupB	P	ICF+
59	PVu	36	F	5 yr	A	E	A	A	A	P	P	A	A	2	Positive	_	Buc mucosa	_	Nil	_	SupB	P	ICF+
60	PVu	65	M	8 mo	A	E	P	A	P	P	P	A	P	5	Positive	_	Tongue	_	Nil	_	SupB	P	ICF+
61	PVu	17	F	3 mo	A	V	P	A	A	P	P	A	A	3	Positive	_	Buc mucosa	_	Nil	_	SupB	P	ICF+
62	PVu	65	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_

S. No.	DIAGNOSIS	AGE	SEX	DURATION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
63	PVu	31	F	11 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_
64	PVu	35	F	2 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_
65	PVu	41	M	1 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_
66	PVu	42	F	5 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_
67	PVu	60	F	3½ mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_
68	PVu	38	F	1 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SupB	_	A	_
69	PVg	50	F	7 yr	P	E	P	A	P	P	P	A	A	4	Negative	Oral	Buc mucosa	1 wk	Nas, Conj, Gen	SupB	SupB	P	
70	PVg	45	F	4 wk	P	E	P	A	A	A	A	A	A	1	Negative	Oral	Lips	3 wk	Nil	SupB	SupB	P	ICF+
71	PVg	42	M	3 mo	P	E	A	A	A	P	A	A	A	1	Negative	Both	Buc mucosa	_	Nil	SupB	SupB	P	ICF+
72	PF	48	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
73	PF	38	F	1 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
74	PF	43	F	2 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
75	PF	72	M	3 wks	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
76	PF	54	F	2½ yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
77	PF	46	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
78	PF	44	M	7 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	

S. No.	DIAGNOSIS	AGE	SEX	DURATION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
79	PF	39	F	1 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
80	PF	53	M	11 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
81	PF	31	F	3 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
82	PF	49	M	2½ yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
83	PE	42	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
84	PE	51	F	1½ yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
85	PE	52	F	15 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
86	PE	48	M	2 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
87	PE	54	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
88	PE	42	F	8 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	ScB	_	A	
89	BP	37	F	6 wk	P	E	A	P	A	P	A	A	A	2	Negative	Skin	Gingiva	2 mo	Nil	SeB	SeB	A	
90	BP	60	M	11 mo	P	B/E	A	P	A	P	A	P	A	3	Negative	Skin	Gingiva	3 mo	Nil	SeB	SeB	A	
91	BP	72	F	2½ yr	P	B/E	A	A	A	P	A	A	A	1	Negative	Oral	Buc mucosa	6 mo	Nil	SeB	SeB	A	
92	BP	24	M	3 yr	P	B	A	A	A	P	A	A	A	1	Negative	Skin	Buc mucosa	1 mo	Nil	SeB	SeB	A	
93	BP	54	F	2 yr	P	E	A	A	A	P	A	A	A	1	Negative	Skin	Buc mucosa	1 mo	Nil	SeB	SeB	A	
94	BP	50	F	6 mo	P	E	A	P	A	A	A	A	A	1	Negative	Oral	Gingiva	2 mo	Nil	SeB	SeB	A	
95	BP	47	F	3 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
96	BP	65	M	10 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
97	BP	60	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
98	BP	80	F	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	

S. No.	DIAGNOSIS	AGE	SEX	DURATION	SKIN	ORAL	LIPS	GINGIVA	TONGUE	BUCCAL MUCOSA	PALATE	FLOOR OF MOUTH	PHARYNX	NO. OF SITES	SCRAPING FOR CANDIDA	FIRST INVOLVED	FIRST AFFECTED IN ORAL CAVITY	TIME INTERVAL	OTHER MUCOSAE	SKIN BIOPSY	MUCOSAL BIOPSY	TZANCK	DIF
99	BP	65	F	9 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
100	BP	60	M	2½ yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
101	BP	85	F	7 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
102	BP	45	M	2 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
103	BP	63	M	1 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
104	BP	53	M	6 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
105	BP	63	F	1 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
106	BP	60	F	2½ yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
107	BP	65	M	3 yr	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
108	BP	61	F	5 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
109	BP	32	F	4 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
110	BP	65	M	15 mo	P	A	A	A	A	A	A	A	A	_	_	_	_	_	Nil	SeB	_	A	
111	DH	50	M	2 yr	P	E	P	A	P	A	A	A	A	2	Negative	Skin	Lips	1½ yr	Nil	SeB	Non specific	A	Neg
112	DH	35	M	3 yr	P	E	P	A	A	A	A	A	A	1	Negative	Skin	Lips	2 yr	Nil	SeB	Non specific	A	Neg
113	DH	65	M	3 mo	P	A	A	A	A	A	A	A	A	_	Negative	_	_	_	Nil	SeB	_	A	
114	DH	65	M	1½ mo	P	A	A	A	A	A	A	A	A	_	Negative	_	_	_	Nil	SeB	_	A	

Drug Reactions

S NO	AGE	SEX	DURATION	DIAGNOSIS	AETIOLOGICAL FACTOR	SKIN LESIONS	% BSA	ORAL LESIONS	LIPS	BUCCAL MUCOSA	PALATE	GINGIVA	TONGUE	FLOOR OF THE MOUTH	FIRST INVOLVED	TIME INTERVAL	OTHER MUCOSAE	INVESTIGATIONS	COMORBID CONDITION
1	23	F	2 wk	EM	Ifosfamide/ Etoposide	P	27%	+	+	_	_	_	_	_	Oral	2 days	_	_	Hodgkin's lymphoma
2	16	M	2 yrs	EM	Amoxicillin	P	36%	+	+	+	_	_	+	+	Oral	3 days	_	_	_
3	60	M	1 mo	EM	Phenytoin	P	72%	+	+	+	_	_	+	_	Oral	2 days	_	_	_
4	28	M	3 yrs	EM	Cephalexin	P	54%	+	+	_	_	_	_	_	Both	_	_	_	_
5	58	M	5 days	SJS	Cefotaxime	P	9%	+	+	_	+	_	_	_	Oral	3 days	_	_	Diabetes mellitus
6	17	M	15 days	SJS	Diclofenac	P	18%	+	+	_	_	_	_	_	Oral	1 day	_	_	_
7	18	F	10 days	SJS	Cotrimoxazole	P	9%	+	+	_	_	_	_	_	Skin	1 day	_	_	_
8	32	M	2 days	TEN	NSAIDS	P	100%	+	+	_	+	_	+	_	Oral	1 day	Genital	HIV +ve	_
9	30	F	1 week	TEN	Diclofenac	P	81%	+	+	_	_	_	_	_	Skin	1 day	Conjunctival	_	_
10	34	F	2 days	TEN	Carbamazepine	P	45%	+	+	_	_	_	_	_	Oral	1 day	_	_	GTCS
11	23	F	5 days	TEN	Carbamazepine	P	46%	+	+	_	_	_	_	_	Oral	3 days	Genital	_	_
12	40	M	1 day	FDE	Paracetamol	P	_	_	_	_	_	_	_	_	_	_	_	_	_

KEY TO MASTER CHART

A. VIRAL INFECTIONS:

HS – Herpes simplex, CP – Varicella, HZ – Herpes zoster, HF – Hand, foot & mouth disease

P – Primary episode, R – Recurrent episode

P – Present, A – Absent

MNG – Multinucleated giant cells, Neg – Negative

B. AUTOIMMUNE BULLOUS DISEASES:

PVu – Pemphigus vulgaris, PVg – Pemphigus vegetans

PF – Pemphigus foliaceous, PE – Pemphigus erythematosus

BP – Bullous pemphigoid, DH – Dermatitis herpetiformis

Oral Morphology: B – Bulla, E – Erosion, V – Vesicle, A- Absent

Duration: wk – week, mo – month, yr – year

Other mucosa: Nas – Nasal mucosa, Gen – Genital mucosa,

Conj – Conjunctiva

Biopsy: SupB – Suprabasal bulla, IeB – Intraepidermal bulla,

ScB – Subcorneal bulla, SeB – Subepidermal bulla

Tzanck: P – Acantholytic cells present, A – Negative

C. DRUG INDUCED:

BSA – Body Surface Area

EM – Erythema multiforme

SJS – Stevens Johnson syndrome

TEN – Toxic epidermal necrolysis.

Proforma

PROFORMA

1. Serial no:
2. Personal details:

   a. Name: d. occupation & income:

   b. Age/sex: e. Address:

   c. OP/IP No:
3. Complaints:
4. H/o presenting illness:

   a. Onset:

   b. Duration:

   c. Symptoms:

   e. Oral lesions preceded/ followed skin lesions

   f. H/o drug intake prior to the onset of lesions

   g. H/o remissions & exacerbations (Rx, sunlight, foods, etc.,)

   h. H/o photosensitivity

   i. H/o loss of weight & appetite

   j. H/o dysphagia, odynophagia

   k. H/o abdominal pain, diarrhoea

   l. H/o sharp teeth & ill fitting dentures.

5. Past history:

   - similar illness:

   - DM, HT, TB

6. Family history:

- similar illness:

7. Personal history:

- diet

- smoking/ alcohol consumption/ pan chewing

8. Menstrual history:

9. General examination:

Pallor/ jaundice/cyanosis/clubbing/pedal edema/lymphadenopathy

10. Vital signs:

PR:

BP:

11. Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

12. Dermatological examination:

a) Skin:

b) Oral cavity:

Vesicle/ bulla/ erosion:	Initial site of involvement:
No:	Bleeding:
Site(s):	Scarring:
Shape:	Hyperpigmentation:
Borders:	Nikolsky’s sign:

c) Genital examination:

d) Other mucosa: Conjunctiva, nasal, oropharyngeal

e) Hair:

f) Nail:

INVESTIGATIONS:

i. Blood:

Hb, TC, DC, ESR, Platelet count

ii. RFT:

iii. LFT:

iv. Blood sugar:

v. HIV-ELISA:

vi. VDRL:

vii. Urine routine:

viii. Chest X-RAY

ix. Serum ANA:

x. Tzanck smear from oral mucosa:

xi. Tongue scraping for candida:

xii. Skin biopsy:

xiii. Mucosal Biopsy:

xiv. Direct immunofluorescence (if done):

xv. HSV IgM ELISA (if done):

xvi. Viral culture (if done):

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. J. Jayasri
PG in MDDVL
Madras Medical College, Chennai -3.

Dear Dr. J. Jayasri

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A Clinico epidemiological study of oral lesions in acquired bullous dermatoses" No. 01112010.

The following members of Ethics Committee were present in the meeting held on 24.11.2010 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K. Rajan, MD	-- Chairperson
2. Prof. J. Mohanasundaram, MD,Ph.D,DNB Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3. Prof. A. Sundaram, MD Vice Principal , MMC, Chennai -3	-- Member Secretary
4. Prof R. Sathianathan, MD Director, Institute of Psychiatry, MMC, Ch-3	-- Member
5. Prof. R. Nandhini, MD Director, Institute of Pharmacology, Ch-3	-- Member
6. Prof. Pregna B. Dolia , MD Director, Institute of Biochemistry, MMC, Ch-3	-- Member
7. Prof. C. Rajendiran , MD Director, Institute of Internal Medicine, MMC, Ch-3	-- Member
8. Thiru. S. Govindasamy BA.BL	-- Lawyer
9. Tmt. Arnold Soulina	-- Social Scientist

We approve the Proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee